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<p>(54) Title: MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS</p> <p>(57) Abstract</p> <p>Nucleic acids encoding mammalian, e.g., primate or rodent receptors, purified receptor proteins and fragments thereof. Antibodies, both polyclonal and monoclonal, are also provided. Methods of using the compositions for both diagnostic and therapeutic utilities are provided.</p>		

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## MAMMALIAN RECEPTOR PROTEINS; RELATED REAGENTS AND METHODS

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## FIELD OF THE INVENTION

The present invention relates to compositions and methods for affecting mammalian physiology, including morphogenesis or immune system function. In particular, it provides nucleic acids, proteins, and antibodies which regulate development and/or the immune system. Various subunits of cytokine receptors, and the matching of subunits in a functional complex are described. Diagnostic and therapeutic uses of these materials are also disclosed.

15

## BACKGROUND OF THE INVENTION

Recombinant DNA technology refers generally to techniques of integrating genetic information from a donor source into vectors for subsequent processing, such as through introduction into a host, whereby the transferred genetic information is copied and/or expressed in the new environment. Commonly, the genetic information exists in the form of complementary DNA (cDNA) derived from messenger RNA (mRNA) coding for a desired protein product. The carrier is frequently a plasmid having the capacity to incorporate cDNA for later replication in a host and, in some cases, actually to control expression of the cDNA and thereby direct synthesis of the encoded product in the host. See, e.g., Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.) vols. 1-3, CSH Press, NY.

For some time, it has been known that the mammalian immune response is based on a series of complex cellular interactions, called the "immune network". Recent research has provided new insights into the inner workings of this network. While it remains clear that much of the immune response does, in fact, revolve around the network-like interactions of lymphocytes,

macrophages, granulocytes, and other cells, immunologists now generally hold the opinion that soluble proteins, known as lymphokines, cytokines, or monokines, play critical roles in controlling these cellular interactions. Thus, there is considerable interest in the isolation, characterization, and mechanisms of action of cell modulatory factors, an understanding of which will lead to significant advancements in the diagnosis and therapy of numerous medical abnormalities, e.g., immune system disorders.

Lymphokines apparently mediate cellular activities in a variety of ways. See, e.g., Paul (ed. 1996) Fundamental Immunology 3d ed., Raven Press, New York; and Thomson (ed. 1994) The Cytokine Handbook 2d ed., Academic Press, San Diego. They have been shown to support the proliferation, growth, and/or differentiation of pluripotential hematopoietic stem cells into vast numbers of progenitors comprising diverse cellular lineages which make up a complex immune system. Proper and balanced interactions between the cellular components are necessary for a healthy immune response. The different cellular lineages often respond in a different manner when lymphokines are administered in conjunction with other agents.

Cell lineages especially important to the immune response include two classes of lymphocytes: B-cells, which can produce and secrete immunoglobulins (proteins with the capability of recognizing and binding to foreign matter to effect its removal), and T-cells of various subsets that secrete lymphokines and induce or suppress the B-cells and various other cells (including other T-cells) making up the immune network. These lymphocytes interact with many other cell types.

Another important cell lineage is the mast cell (which has not been positively identified in all mammalian species), which is a granule-containing connective tissue cell located proximal to capillaries throughout the body. These cells are found in especially



high concentrations in the lungs, skin, and gastrointestinal and genitourinary tracts. Mast cells play a central role in allergy-related disorders, particularly anaphylaxis as follows: when selected  
5 antigens crosslink one class of immunoglobulins bound to receptors on the mast cell surface, the mast cell degranulates and releases mediators, e.g., histamine, serotonin, heparin, and prostaglandins, which cause allergic reactions, e.g., anaphylaxis.

10 Research to better understand and treat various immune disorders has been hampered by the general inability to maintain cells of the immune system in vitro. Immunologists have discovered that culturing many of these cells can be accomplished through the use of T-  
15 cell and other cell supernatants, which contain various growth factors, including many of the lymphokines.

Various growth and regulatory factors exist which modulate morphogenetic development. This includes, e.g., the Toll ligands, which signal through binding to  
20 receptors which share structural, and mechanistic, features characteristic of the IL-1 receptors. See, e.g., Lemaitre, et al. (1996) Cell 86:973-983; and Belvin and Anderson (1996) Ann. Rev. Cell & Devel. Biol. 12:393-416. Other receptors for cytokines are also known.  
25 Often, there are at least two critical subunits in the functional receptor. See, e.g., Gonda and D'Andrea (1997) Blood 89:355-369; Presky, et al. (1996) Proc. Nat'l Acad. Sci. USA 93:14002-14007; Drachman and Kaushansky (1995) Curr. Opin. Hematol. 2:22-28; Theze  
30 (1994) Eur. Cytokine Netw. 5:353-368; and Lemmon and Schlessinger (1994) Trends Biochem. Sci. 19:459-463.

From the foregoing, it is evident that the discovery and development of new soluble proteins and their receptors, including ones similar to lymphokines, should  
35 contribute to new therapies for a wide range of degenerative or abnormal conditions which directly or indirectly involve development, differentiation, or function, e.g., of the immune system and/or hematopoietic

cells. In particular, the discovery and understanding of novel receptors for lymphokine-like molecules which enhance or potentiate the beneficial activities of other lymphokines would be highly advantageous. The present invention provides new receptors for ligands exhibiting similarity to cytokine like compositions and related compounds, and methods for their use.

#### SUMMARY OF THE INVENTION

The present invention is directed to a novel receptor related to cytokine receptors, e.g., primate or rodent, cytokine receptor like molecular structures, designated DNAX Cytokine Receptor Subunit 1 (DCRS1), and their biological activities. The matching of subunits in a functional receptor, and ligand identification are described. It includes nucleic acids coding for the combinations of polypeptides themselves and methods for their production and use. The nucleic acids of the invention are characterized, in part, by their homology to cloned complementary DNA (cDNA) sequences enclosed herein.

In certain embodiments, the invention provides a composition of matter selected from the group of: a substantially pure or recombinant DCRS1 protein or peptide exhibiting at least about 85% sequence identity over a length of at least about 12 amino acids to SEQ ID NO: 13 or 4 or 15; a natural sequence DCRS1 comprising SEQ ID NO: 13 or 4 or 15; and a fusion protein comprising DCRS1 sequence. Preferably, the substantially pure or isolated protein comprises a segment exhibiting sequence identity to a corresponding portion of a DCRS1, wherein: the homology is at least about 90% identity and the portion is at least about 9 amino acids; the homology is at least about 80% identity and the portion is at least about 17 amino acids; or the homology is at least about 70% identity and the portion is at least about 25 amino acids. In specific embodiments, the composition of matter is DCRS1, which comprises a mature sequence of

Table 1; or exhibits a non-glycosylated DCRS1; or the composition of matter may be a protein or peptide which: is from a warm blooded animal selected from a mammal, including a primate or rodent, such as a human or mouse; comprises at least one polypeptide segment of SEQ ID NO: 13 or 4 or 15; exhibits a plurality of portions exhibiting said identity; is a natural allelic variant of DCRS1; has a length at least about 30 amino acids; exhibits at least two non-overlapping epitopes which are specific for a primate or rodent DCRS1; exhibits a sequence identity at least about 90% over a length of at least about 20 amino acids to a primate or rodent DCRS1; is glycosylated; has a molecular weight of at least 100 kD with natural glycosylation; is a synthetic polypeptide; is attached to a solid substrate; is conjugated to another chemical moiety; is a 5-fold or less substitution from natural sequence; or is a deletion or insertion variant from a natural sequence.

Other embodiments include a composition comprising: a sterile DCRS1 protein or peptide; or the DCRS1 protein or peptide and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

In certain fusion protein embodiments, the invention provides a fusion protein comprising: mature protein sequence of Table 1; a detection or purification tag, including a FLAG, His6, or Ig sequence; or sequence of another receptor protein.

Various kit embodiments include a kit comprising a DCRS1 protein or polypeptide, and: a compartment comprising the protein or polypeptide; and/or instructions for use or disposal of reagents in the kit.

Binding compound embodiments include those comprising an antigen binding site from an antibody, which specifically binds to a natural DCRS1 protein, wherein: the protein is a primate protein; the binding compound is an Fv, Fab, or Fab2 fragment; the binding

compound is conjugated to another chemical moiety; or the antibody: is raised against a peptide sequence of a mature polypeptide of Table 1; is raised against a mature DCRS1; is raised to a purified human or mouse DCRS1; is immunoselected; is a polyclonal antibody; binds to a denatured DCRS1; exhibits a  $K_d$  to antigen of at least 30  $\mu M$ ; is attached to a solid substrate, including a bead or plastic membrane; is in a sterile composition; or is detectably labeled, including a radioactive or fluorescent label. A binding composition kit often comprises the binding compound, and: a compartment comprising said binding compound; and/or instructions for use or disposal of reagents in the kit. Often the kit is capable of making a qualitative or quantitative analysis.

Other compositions include a composition comprising: a sterile binding compound, or the binding compound and a carrier, wherein the carrier is: an aqueous compound, including water, saline, and/or buffer; and/or formulated for oral, rectal, nasal, topical, or parenteral administration.

Nucleic acid embodiments include an isolated or recombinant nucleic acid encoding a DCRS1 protein or peptide or fusion protein, wherein: the DCRS1 is from a mammal; or the nucleic acid: encodes an antigenic peptide sequence of Table 1; encodes a plurality of antigenic peptide sequences of Table 1; exhibits at least about 80% identity to a natural cDNA encoding said segment; is an expression vector; further comprises an origin of replication; is from a natural source; comprises a detectable label; comprises synthetic nucleotide sequence; is less than 6 kb, preferably less than 3 kb; is from a mammal, including a primate; comprises a natural full length coding sequence; is a hybridization probe for a gene encoding said DCRS1; or is a PCR primer, PCR product, or mutagenesis primer. A cell, tissue, or organ comprising such a recombinant nucleic acid is also provided. Preferably, the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an

insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell. Kits are provided comprising such nucleic acids, and: a compartment comprising said nucleic acid; a compartment further comprising a primate or  
5 rodent DCRS1 protein or polypeptide; and/or instructions for use or disposal of reagents in the kit. Often, the kit is capable of making a qualitative or quantitative analysis.

Other embodiments include a nucleic acid which:  
10 hybridizes under wash conditions of 30° C and less than 2M salt to SEQ ID NO: 12 or 3 or 14; or exhibits at least about 85% identity over a stretch of at least about 30 nucleotides to a primate DCRS1. Preferably, such nucleic acid will have such properties, wherein: wash conditions  
15 are at 45° C and/or 500 mM salt; or the identity is at least 90% and/or the stretch is at least 55 nucleotides.

More preferably, the wash conditions are at 55° C and/or 150 mM salt; or the identity is at least 95% and/or the stretch is at least 75 nucleotides.

20 The invention also provides a method of modulating physiology or development of a cell or tissue culture cells comprising contacting the cell with an agonist or antagonist of a mammalian, e.g., primate or rodent DCRS1. It also provides cells cotransfected with a nucleic acid  
25 encoding DCRS1 and another cytokine receptor subunit, e.g., DSRS1. This will allow pairing of subunits to determine the physiological receptor pairs for various cytokine ligands.

The present invention provides various compositions,  
30 e.g., comprising both a DSRS1 protein and an isolated or recombinant DCRS1 protein; both an isolated or recombinant DSRS1 protein and a DCRS1 protein; or both a substantially pure or recombinant IL-B30 protein and a DCRS1 protein. In certain embodiments, the DSRS1 protein  
35 has sequence of mature SEQ ID NO: 9 or 11; the DCRS1 protein has sequence of mature SEQ ID NO: 13 or 15; or the IL-B30 has sequence of mature SEQ ID NO: 17 or 19. In other embodiments, at least one of the proteins: is

unglycosylated; is made with synthetic methods; has a detectable label; is attached to a solid substrate; or is conjugated to another chemical moiety.

In other forms, the invention provides a composition  
5 comprising: a substantially pure DCRS1 protein and: a  
DSRS1 protein or an IL-B30 cytokine protein; or a DCRS1  
protein and a substantially pure: DSRS1 protein or IL-B30  
cytokine protein. Preferred forms combining the DCRS1  
and the DSRS1 proteins are those where the proteins  
10 combine to bind IL-B30 with high affinity. Yet other  
forms include sterile compositions, as described.

Kit embodiments include such compositions combined  
with: a compartment comprising two or more of the  
proteins; a compartment comprising a soluble receptor  
15 alpha subunit; a compartment comprising an IL-B30  
cytokine protein; or instructions for use or disposal of  
reagents in the kit.

Binding composition embodiments include those  
comprising the antigen binding sites from antibodies,  
20 which antibodies bind to an epitope found on a  
composition described above, but not on separate proteins  
thereof. Various embodiments include where: the DCRS1  
is: a primate protein, a purified human or mouse DCRS1,  
or a mature polypeptide of Table 1; the DSRS1 is: a  
25 primate protein, a purified human or mouse DSRS1, or a  
mature polypeptide of Table 4; or the IL-B30 is: a  
primate protein, a purified human or mouse IL-B30, or a  
mature polypeptide of Table 6. Other embodiments include  
those where the binding composition: is in a container;  
30 is an Fv, Fab, or Fab2 fragment; is conjugated to another  
chemical moiety; is immunoselected; is a polyclonal  
antibody; exhibits a Kd to antigen of at least 30  $\mu$ M; is  
attached to a solid substrate, including a bead or  
plastic membrane; is in a sterile composition; or is  
35 detectably labeled, including a radioactive or  
fluorescent label.

Kit embodiments which comprise the binding  
compositions further include, e.g., a compartment

comprising the binding composition; a compartment comprising the DCRS1, DSRS1, or IL-B30 protein; or instructions for use or disposal of reagents in the kit.

Certain nucleic acid composition are provided, e.g.,  
5 an isolated or recombinant nucleic acid encoding both: a DSRS1 protein and a DCRS1 protein; a DSRS1 protein and an IL-B30 protein; or a DCRS1 protein and an IL-B30 protein. Preferred embodiments are those nucleic acids which encode both a DCRS1 protein and a DSRS1 protein; or both  
10 a DSRS1 protein and an IL-B30, e.g., in a fusion protein. Other preferred embodiments are those nucleic acids which are expression vectors. Preferably, the DSRS1 protein has sequence of mature SEQ ID NO: 9 or 11; the DCRS1 protein has sequence of mature SEQ ID NO: 13 or 15; or  
15 the IL-B30 has sequence of mature SEQ ID NO: 17 or 19. Specific embodiments are those comprising the coding portion of: SEQ ID NO: 8 or 10; SEQ ID NO: 12 or 14; or SEQ ID NO: 16 or 18.

Transformed cells with the nucleic acids are  
20 provided, including where the cell is: a prokaryotic cell; a eukaryotic cell; a bacterial cell; a yeast cell; an insect cell; a mammalian cell; a mouse cell; a primate cell; or a human cell.

Various methods are also provided, e.g., a method of  
25 producing a receptor complex, comprising culturing a described transformed cell of in an environment resulting in expression of the DCRS1 and the DSRS1 proteins, thereby forming the receptor complex; or of screening for ligands for a receptor complex comprising the DCRS1 and  
30 the DSRS1 proteins, comprising screening a library of compounds for binding to the described cell.

#### DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

##### 35 I. General

The present invention provides the amino acid sequence and DNA sequence of mammalian, herein primate, cytokine receptor-like subunit molecules, this one

designated DNAX Cytokine Receptor Subunit 1 (DCRS1) having particular defined properties, both structural and biological. Various cDNAs encoding these molecules were obtained from primate, e.g., human, cDNA sequence  
 5 libraries. Other primate or other mammalian counterparts would also be desired.

Some of the standard methods applicable are described or referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring  
 10 Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology, Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and periodic supplements) Current Protocols  
 15 in Molecular Biology, Greene/Wiley, New York; each of which is incorporated herein by reference.

Partial nucleotide (SEQ ID NO: 1) and corresponding amino acid sequence (SEQ ID NO: 2) of a human DCRS1 coding segment is shown in Table 1, with supplementary  
 20 sequence provided in SEQ ID NO: 12 and 13. Partial mouse sequence is provided (SEQ ID NO: 3 and 4), with supplementary sequence in SEQ ID NO: 14 and 15.

Table 1: Partial nucleotide and polypeptide sequences of DNAX Cytokine Receptor Subunit like embodiments (DCRS1). Primate, e.g., human embodiment (see SEQ ID NO: 1 and 2).

30	gtc tgg ccc ccc gtc ttc gtg aac cta gaa acc caa atg aag cca aac	48
	Val Trp Pro Pro Val Phe Val Asn Leu Glu Thr Gln Met Lys Pro Asn	
	1 5 10 15	
35	gcc ccc cgg ctg ggc cct gac gtg gac ttt tcc gag gat gac ccc ctg	96
	Ala Pro Arg Leu Gly Pro Asp Val Asp Phe Ser Glu Asp Asp Pro Leu	
	20 25 30	
40	gag gcc act gtc cat tgg gcc cca cct aca tgg cca tct cat aaa gtt	144
	Glu Ala Thr Val His Trp Ala Pro Pro Thr Trp Pro Ser His Lys Val	
	35 40 45	
45	ctg atc tgc cag ttc cac tac cga aga tgt cag gag gcg gcc tgg acc	192
	Leu Ile Cys Gln Phe His Tyr Arg Arg Cys Gln Glu Ala Ala Trp Thr	
	50 55 60	
45	ctg ctg gaa ccg gag ctg aag acc ata ccc ctg acc cct gtt gag atc	240
	Leu Leu Glu Pro Glu Leu Lys Thr Ile Pro Leu Thr Pro Val Glu Ile	
	65 70 75 80	



	caa gat ttg gag cta gcc act ggc tac aaa gtg tat ggc cgc tgc cgg	288
	Gln Asp Leu Glu Leu Ala Thr Gly Tyr Lys Val Tyr Gly Arg Cys Arg	
	85 90 95	
5	atg gag aaa gaa gag gat ttg tgg ggc gag tgg agc ccc att ttg tcc	336
	Met Glu Lys Glu Glu Asp Leu Trp Gly Glu Trp Ser Pro Ile Leu Ser	
	100 105 110	
10	ttc cag aca ccg cct tct gct cca aaa gat gtg tgg gta tca ggg aac	384
	Phe Gln Thr Pro Pro Ser Ala Pro Lys Asp Val Trp Val Ser Gly Asn	
	115 120 125	
15	ctc tgt ggg acg cct gga gga gag gaa cct ttg ctt cta tgg aag gcc	432
	Leu Cys Gly Thr Pro Gly Gly Glu Glu Pro Leu Leu Leu Trp Lys Ala	
	130 135 140	
20	cca ggg ccc tgt gtg cag gtg agc tac aaa gtc tgg ttc tgg gtt gga	480
	Pro Gly Pro Cys Val Gln Val Ser Tyr Lys Val Trp Phe Trp Val Gly	
	145 150 155 160	
25	ggt cgt gag ctg agt cca gaa gga att acc tgc tgc tgc tcc cta att	528
	Gly Arg Glu Leu Ser Pro Glu Gly Ile Thr Cys Cys Cys Ser Leu Ile	
	165 170 175	
30	ccc agt ggg gcg gag tgg gcc agg gtg tcc gct gtc aac gcc aca agc	576
	Pro Ser Gly Ala Glu Trp Ala Arg Val Ser Ala Val Asn Ala Thr Ser	
	180 185 190	
35	gag gag cct ctc acc aac ctc tct ttg gtc tgc ttg gat tca gcc tct	624
	Trp Glu Pro Leu Thr Asn Leu Ser Leu Val Cys Leu Asp Ser Ala Ser	
	195 200 205	
40	gcc ccc cgt agc gtg gca gtc agc agc atc gct ggg agc acg gag cta	672
	Ala Pro Arg Ser Val Ala Val Ser Ser Ile Ala Gly Ser Thr Glu Leu	
	210 215 220	
45	ctg gtg acc tgg caa ccg ggg cct ggg gaa cca ctg gag cat gta atg	720
	Leu Val Thr Trp Gln Pro Gly Pro Gly Glu Pro Leu Glu His Val Met	
	225 230 235 240	
50	gac tgg gct cga gat ggg gac ccc ctg gag aaa ctc aac tgg gtc cgg	768
	Asp Trp Ala Arg Asp Gly Asp Pro Leu Glu Lys Leu Asn Trp Val Arg	
	245 250 255	
55	ctt ccc cct ggg aac ctc agt gct ctg tta cca ggg aat ttc act gtc	816
	Leu Pro Pro Gly Asn Leu Ser Ala Leu Leu Pro Gly Asn Phe Thr Val	
	260 265 270	
60	ggg gtc ccc tat cga atc act gtg acc gca gtc tct gct tca ggc ttg	864
	Gly Val Pro Tyr Arg Ile Thr Val Thr Ala Val Ser Ala Ser Gly Leu	
	275 280 285	
65	gcc tct gca tcc tcc gtc tgg ggg ttc agg gag gaa tta gca ccc cta	912
	Ala Ser Ala Ser Ser Val Trp Gly Phe Arg Glu Glu Leu Ala Pro Leu	
	290 295 300	
70	gtg ggg cca acg ctt tgg cga ctc caa gat gcc cct cca ggg acc ccc	960
	Val Gly Pro Thr Leu Trp Arg Leu Gln Asp Ala Pro Pro Gly Thr Pro	
	305 310 315 320	

5	gcc ata gcg tgg gga gag gtc cca agg cac cag ctt cga ggc cac ctc	1008
	Ala Ile Ala Trp Gly Glu Val Pro Arg His Gln Leu Arg Gly His Leu	
	325 330 335	
10	acc cac tac acc ttg tgt gca cag agt gga acc agc ccc tcc gtc tgc	1056
	Thr His Tyr Thr Leu Cys Ala Gln Ser Gly Thr Ser Pro Ser Val Cys	
	340 345 350	
15	atg aat gtg agt ggc aac aca cag agt gtc acc ctg cct gac ctt cct	1104
	Met Asn Val Ser Gly Asn Thr Gln Ser Val Thr Leu Pro Asp Leu Pro	
	355 360 365	
20	tgg ggt ccc tgt gag ctg tgg gtg aca gca tct acc atc gct gga cag	1152
	Trp Gly Pro Cys Glu Leu Trp Val Thr Ala Ser Thr Ile Ala Gly Gln	
	370 375 380	
25	ggc cct cct ggt ccc atc ctc cgg ctt cat cta cca gat aac acc ctg	1200
	Gly Pro Pro Gly Pro Ile Leu Arg Leu His Leu Pro Asp Asn Thr Leu	
	385 390 395 400	
30	agg tgg aaa gtt ctg ccg ggc atc cta ttc ttg tgg ggc ttg ttc ctg	1248
	Arg Trp Lys Val Leu Pro Gly Ile Leu Phe Leu Trp Gly Leu Phe Leu	
	405 410 415	
35	ttg ggg tgt ggc ctg agc ctg gcc acc tct gga agg tgc tac cac cta	1296
	Leu Gly Cys Gly Leu Ser Leu Ala Thr Ser Gly Arg Cys Tyr His Leu	
	420 425 430	
40	agg cac aaa gtg ctg ccc cgc tgg gtc tgg gag aaa gtt cct gat cct	1344
	Arg His Lys Val Leu Pro Arg Trp Val Trp Glu Lys Val Pro Asp Pro	
	435 440 445	
45	gcc aac agc agt tca ggc cag ccc cac atg gag caa gta cct gag gcc	1392
	Ala Asn Ser Ser Ser Gly Gln Pro His Met Glu Gln Val Pro Glu Ala	
	450 455 460	
50	cag ccc ctt ggg gac ttg ccc atc ctg gaa gtg gag gag atg gag ccc	1440
	Gln Pro Leu Gly Asp Leu Pro Ile Leu Glu Val Glu Glu Met Glu Pro	
	465 470 475 480	
55	ccg ccg gtt atg gag tcc tcc cag ccc gcc cag gcc acc gcc ccg ctt	1488
	Pro Pro Val Met Glu Ser Ser Gln Pro Ala Gln Ala Thr Ala Pro Leu	
	485 490 495	
60	gac tct ggg tat gag aag cac ttc ctg ccc aca cct gag gag ctg ggc	1536
	Asp Ser Gly Tyr Glu Lys His Phe Leu Pro Thr Pro Glu Glu Leu Gly	
	500 505 510	
65	ctt ctg ggg ccc ccc agg cca cag gtt ctg gcc tgaaccacac gtctggctgg	1589
	Leu Leu Gly Pro Pro Arg Pro Gln Val Leu Ala	
	515 520	
70	gggctgccag ccaggctaga gggatgctca tgcaggttgc accccagtcc tggattagcc	1649
	ctcttgatgg atgaagacac tgaggactca gagaggctga gtcacttacc tgaggacacc	1709
75	cagccaggca gagctgggat tgaaggaccc ctatagagaa gggcttggcc cccatgggga	1769
	agacacggat ggaaggtgga gcaaaggaaa atacatgaaa ttgagagtgg cagctgcctg	1829
	ccaaaatctg ttccgctgta acagaactga atttggaccc cagcacagtg gctcacgcct	1889

gtaatcccag cactttggca ggccaaggtg gaaggatcac ttagagctag gagtttgaga 1949  
 5 ccagcctggg caatatagca agaccctca ctacaaaaat aaaacatcaa aaacaaaaac 2009  
 aattagctgg gcatgatggc acacacctgt agtccgagcc acttgggagg ctgaggtggg 2069  
 aggatcggtt gagcccagga gtttgaagct gcagggacct ctgattgcac cactgcactc 2129  
 10 caggctgggt aacagaatga gacctatyt caaaaataaa caaactaatw aaarmaaaaa 2189  
 aaaaaaamwm raraaaaaaa aaaa 2213

15 Partial "downstream" sequences of rodent, e.g., mouse, embodiment  
 of DCRS1 (SEQ ID NO: 3 and 4):

20 aaa gga ggg gtc ccc tat cga att aca gtg act gca gta tac tct gga 48  
 Lys Gly Gly Val Pro Tyr Arg Ile Thr Val Thr Ala Val Tyr Ser Gly  
 1 5 10 15

25 gga tta gct gct gca ccc tca gtt tgg gga ttc aga gag gag tta gta 96  
 Gly Leu Ala Ala Ala Pro Ser Val Trp Gly Phe Arg Glu Glu Leu Val  
 20 25 30

30 ccc ctt gct ggg cca gca gtt tgg cga ctt cca gat gac ccc cca ggg 144  
 Pro Leu Ala Gly Pro Ala Val Trp Arg Leu Pro Asp Asp Pro Pro Gly  
 35 40 45

35 aca cct gtt gta gcc tgg gga gaa gta cca aga cac cag ctc aga ggc 192  
 Thr Pro Val Val Ala Trp Gly Glu Val Pro Arg His Gln Leu Arg Gly  
 50 55 60

40 cag gct act cac tac acc ttc tgc ata cag agc aga ggc ctc tcc act 240  
 Gln Ala Thr His Tyr Thr Phe Cys Ile Gln Ser Arg Gly Leu Ser Thr  
 65 70 75 80

45 gtc tgc agg aac gtg agc agt caa acc cag act gcc act ctg ccc aac 288  
 Val Cys Arg Asn Val Ser Ser Gln Thr Gln Thr Ala Thr Leu Pro Asn  
 85 90 95

50 ctt cac tcg ggt tcc ttc aag ctg tgg gtg acg gtg tcc acc gtt gca 336  
 Leu His Ser Gly Ser Phe Lys Leu Trp Val Thr Val Ser Thr Val Ala  
 100 105 110

55 gga cag ggc cca cct ggt ccc gac ctt tca ctt cac cta cca gat aat 384  
 Gly Gln Gly Pro Pro Gly Pro Asp Leu Ser Leu His Leu Pro Asp Asn  
 115 120 125

60 agg atc agg tgg aaa gct ctg ccc tgg ttt ctg tcc ctg tgg ggt ttg 432  
 Arg Ile Arg Trp Lys Ala Leu Pro Trp Phe Leu Ser Leu Trp Gly Leu  
 130 135 140

65 ctt ctg atg ggc tgt ggc ctg agc ctg gcc agt acc agg tgc cta cag 480  
 Leu Leu Met Gly Cys Gly Leu Ser Leu Ala Ser Thr Arg Cys Leu Gln  
 145 150 155 160

70 gcc agg tgc tta cac tgg cga cac aag ttg ctt ccc cag tgg atc tgg 528  
 Ala Arg Cys Leu His Trp Arg His Lys Leu Leu Pro Gln Trp Ile Trp  
 165 170 175

gag agg gtt cct gat cct gcc aac agc aat tct ggg caa cct tac atc 576  
 Glu Arg Val Pro Asp Pro Ala Asn Ser Asn Ser Gly Gln Pro Tyr Ile  
 180 185 190

5 aag gag gtg agc ctg ccc caa ccg ccc aag gac gga ccc atc ctg gag 624  
 Lys Glu Val Ser Leu Pro Gln Pro Pro Lys Asp Gly Pro Ile Leu Glu  
 195 200 205

10 gtg gag gaa gtg gag cta cag cct gtt gtg gag tcc cct aaa gcc tct 672  
 Val Glu Glu Val Glu Leu Gln Pro Val Val Glu Ser Pro Lys Ala Ser  
 210 215 220

15 gcc ccg att tac tct ggg tat gag aaa cac ttc ctg ccc aca cca gag 720  
 Ala Pro Ile Tyr Ser Gly Tyr Glu Lys His Phe Leu Pro Thr Pro Glu  
 225 230 235 240

20 gag ctg ggc ctt cta gtc tgatctgctt acggctaggg gctgtacccc 768  
 Glu Leu Gly Leu Leu Val  
 245

tatcttgggc tagacgtttt tgtattttta gatttttgag acaggatctc actatggctg 828

25 gcctggaact tgatataaca accaggctgg cctggaactc accaagactc acctgggtttt 888  
 gccttccaag gactgagaag aaatgagtgt gccgcctccc gccaaccag cttttgcttt 948  
 ccttgccctct gggctcttggg catctgtttg ttactgcaga agaatcagtg agctcacagc 1008

30 ctgcaacttg tgatcctccc tgctgcagca tccccagagc tgggattaca ggtgtgcgtc 1068  
 acttcatcga gtcataactt ttgattctag tgagaataac taccaggcag gctatgaggt 1128  
 ggtgactcga aagacacatt caaggaccta aagtgggttaa gagcctgtgt tttcttgagc 1188

35 tagaccaaag tttggttccc tgcccttgca aaggacacac gttcagtttc cagcaccac 1248  
 agggcagttc agaatcacct gtaactccag gtccaaggaa tccaatgcc tcttctggct 1308  
 tctgtgagcc ccgcacacac atgggttactt atgcaccgaa aaacacacgc ataaaataaa 1368

40 aataaataaa taaataaaaa taaattaata aataatcttt tttttcttaa aaaaaaaaaa 1428  
 aaa 1431

45 supplementary primate, e.g., human, DCRS1 sequence (SEQ ID NO: 12  
 and 13):

50 atg cgg gga ggc agg ggc gcc cct ttc tgg ctg tgg ccg ctg ccc aag 48  
 Met Arg Gly Gly Arg Gly Ala Pro Phe Trp Leu Trp Pro Leu Pro Lys  
 1 5 10 15

55 ctg gcg ctg ctg cct ctg ttg tgg gtg ctt ttc cag cgg acg cgt ccc 96  
 Leu Ala Leu Leu Pro Leu Leu Trp Val Leu Phe Gln Arg Thr Arg Pro  
 20 25 30

60 cag ggc agc gcc ggg cca ctg cag tgc tac gga gtt gga ccc ttg ggc 144  
 Gln Gly Ser Ala Gly Pro Leu Gln Cys Tyr Gly Val Gly Pro Leu Gly  
 35 40 45

5	gac ttg aac tgc tgc tgg gag cct ctt ggg gac ctg gga gcc ccc tcc																192
	Asp	Leu	Asn	Cys	Ser	Trp	Glu	Pro	Leu	Gly	Asp	Leu	Gly	Ala	Pro	Ser	
	50						55					60					
10	gag tta cac ctc cag agc caa aag tac cgt tcc aac aaa acc cag act																240
	Glu	Leu	His	Leu	Gln	Ser	Gln	Lys	Tyr	Arg	Ser	Asn	Lys	Thr	Gln	Thr	
	65					70				75					80		
15	gtg gca gtg gca gcc gga cgg agc tgg gtg gcc att cct cgg gaa cag																288
	Val	Ala	Val	Ala	Ala	Gly	Arg	Ser	Trp	Val	Ala	Ile	Pro	Arg	Glu	Gln	
					85					90					95		
20	ctc acc atg tct gac aaa ctc ctt gtc tgg ggc ayt aag gca ggc cag																336
	Leu	Thr	Met	Ser	Asp	Lys	Leu	Leu	Val	Trp	Gly	Xaa	Lys	Ala	Gly	Gln	
				100					105					110			
25	cct ctc tgg ccc ccc gtc ttc gtg aac cta gaa acc caa atg aag cca																384
	Pro	Leu	Trp	Pro	Pro	Val	Phe	Val	Asn	Leu	Glu	Thr	Gln	Met	Lys	Pro	
			115					120					125				
30	aac gcc ccc cgg ctg ggc cct gac gtg gac ttt tcc gag gat gac ccc																432
	Asn	Ala	Pro	Arg	Leu	Gly	Pro	Asp	Val	Asp	Phe	Ser	Glu	Asp	Asp	Pro	
		130					135					140					
35	ctg gag gcc act gtc cat tgg gcc cca cct aca tgg cca tct cat aaa																480
	Leu	Glu	Ala	Thr	Val	His	Trp	Ala	Pro	Pro	Thr	Trp	Pro	Ser	His	Lys	
	145					150					155					160	
40	gtt ctg atc tgc cag ttc cac tac cga aga tgt cag gag gcg gcc tgg																528
	Val	Leu	Ile	Cys	Gln	Phe	His	Tyr	Arg	Arg	Cys	Gln	Glu	Ala	Ala	Trp	
					165					170					175		
45	acc ctg ctg gaa ccg gag ctg aag acc ata ccc ctg acc cct gtt gag																576
	Thr	Leu	Leu	Glu	Pro	Glu	Leu	Lys	Thr	Ile	Pro	Leu	Thr	Pro	Val	Glu	
				180					185						190		
50	atc caa gat ttg gag cta gcc act ggc tac aaa gtg tat ggc cgc tgc																624
	Ile	Gln	Asp	Leu	Glu	Leu	Ala	Thr	Gly	Tyr	Lys	Val	Tyr	Gly	Arg	Cys	
			195					200					205				
55	cgg atg gag aaa gaa gag gat ttg tgg ggc gag tgg agc ccc att ttg																672
	Arg	Met	Glu	Lys	Glu	Glu	Asp	Leu	Trp	Gly	Glu	Trp	Ser	Pro	Ile	Leu	
		210					215					220					
60	tcc ttc cag aca ccg cct tct gct cca aaa gat gtg tgg gta tca ggg																720
	Ser	Phe	Gln	Thr	Pro	Pro	Ser	Ala	Pro	Lys	Asp	Val	Trp	Val	Ser	Gly	
						230					235					240	
65	aac ctc tgt ggg acg cct gga gga gag gaa cct ttg ctt cta tgg aag																768
	Asn	Leu	Cys	Gly	Thr	Pro	Gly	Gly	Glu	Glu	Pro	Leu	Leu	Leu	Trp	Lys	
					245					250					255		
70	gcc cca ggg ccc tgt gtg cag gtg agc tac aaa gtc tgg ttc tgg gtt																816
	Ala	Pro	Gly	Pro	Cys	Val	Gln	Val	Ser	Tyr	Lys	Val	Trp	Phe	Trp	Val	
				260					265						270		
75	gga ggt cgt gag ctg agt cca gaa gga att acc tgc tgc tgc tcc cta																864
	Gly	Gly	Arg	Glu	Leu	Ser	Pro	Glu	Gly	Ile	Thr	Cys	Cys	Cys	Ser	Leu	
			275					280					285				

5	att ccc agt ggg gcg gag tgg gcc agg gtg tcc gct gtc aac gcc aca	912
	Ile Pro Ser Gly Ala Glu Trp Ala Arg Val Ser Ala Val Asn Ala Thr 290 295 300	
10	agc tgg gag cct ctc acc aac ctc tct ttg gtc tgc ttg gat tca gcc	960
	Ser Trp Glu Pro Leu Thr Asn Leu Ser Leu Val Cys Leu Asp Ser Ala 305 310 315 320	
15	tct gcc ccc cgt agc gtg gca gtc agc agc atc gct ggg agc acg gag	1008
	Ser Ala Pro Arg Ser Val Ala Val Ser Ser Ile Ala Gly Ser Thr Glu 325 330 335	
20	cta ctg gtg acc tgg caa ccg ggg cct ggg gaa cca ctg gag cat gta	1056
	Leu Leu Val Thr Trp Gln Pro Gly Pro Gly Glu Pro Leu Glu His Val 340 345 350	
25	atg gac tgg gct cga gat ggg gac ccc ctg gag aaa ctc aac tgg gtc	1104
	Met Asp Trp Ala Arg Asp Gly Asp Pro Leu Glu Lys Leu Asn Trp Val 355 360 365	
30	cgg ctt ccc cct ggg aac ctc agt gct ctg tta cca ggg aat ttc act	1152
	Arg Leu Pro Pro Gly Asn Leu Ser Ala Leu Leu Pro Gly Asn Phe Thr 370 375 380	
35	gtc ggg gtc ccc tat cga atc act gtg acc gca gtc tct gct tca ggc	1200
	Val Gly Val Pro Tyr Arg Ile Thr Val Thr Ala Val Ser Ala Ser Gly 385 390 395 400	
40	ttg gcc tct gca tcc tcc gtc tgg ggg ttc agg gag gaa tta gca ccc	1248
	Leu Ala Ser Ala Ser Val Trp Gly Phe Arg Glu Glu Leu Ala Pro 405 410 415	
45	cta gtg ggg cca acg ctt tgg cga ctc caa gat gcc cct cca ggg acc	1296
	Leu Val Gly Pro Thr Leu Trp Arg Leu Gln Asp Ala Pro Pro Gly Thr 420 425 430	
50	ccc gcc ata gcg tgg gga gag gtc cca agg cac cag ctt cga ggc cac	1344
	Pro Ala Ile Ala Trp Gly Glu Val Pro Arg His Gln Leu Arg Gly His 435 440 445	
55	ctc acc cac tac acc ttg tgt gca cag agt gga acc agc ccc tcc gtc	1392
	Leu Thr His Tyr Thr Leu Cys Ala Gln Ser Gly Thr Ser Pro Ser Val 450 455 460	
60	tgc atg aat gtg agt ggc aac aca cag agt gtc acc ctg cct gac ctt	1440
	Cys Met Asn Val Ser Gly Asn Thr Gln Ser Val Thr Leu Pro Asp Leu 465 470 475 480	
65	cct tgg ggt ccc tgt gag ctg tgg gtg aca gca tct acc atc gct gga	1488
	Pro Trp Gly Pro Cys Glu Leu Trp Val Thr Ala Ser Thr Ile Ala Gly 485 490 495	
70	cag ggc cct cct ggt ccc atc ctc cgg ctt cat cta cca gat aac acc	1536
	Gln Gly Pro Pro Gly Pro Ile Leu Arg Leu His Leu Pro Asp Asn Thr 500 505 510	
75	ctg agg tgg aaa gtt ctg ccg ggc atc cta ttc ttg tgg ggc ttg ttc	1584
	Leu Arg Trp Lys Val Leu Pro Gly Ile Leu Phe Leu Trp Gly Leu Phe 515 520 525	

	ctg ttg ggg tgt ggc ctg agc ctg gcc acc tct gga agg tgc tac cac	1632
	Leu Leu Gly Cys Gly Leu Ser Leu Ala Thr Ser Gly Arg Cys Tyr His	
	530 535 540	
5	cta agg cac aaa gtg ctg ccc cgc tgg gtc tgg gag aaa gtt cct gat	1680
	Leu Arg His Lys Val Leu Pro Arg Trp Val Trp Glu Lys Val Pro Asp	
	545 550 555 560	
10	cct gcc aac agc agt tca ggc cag ccc cac atg gag caa gta cct gag	1728
	Pro Ala Asn Ser Ser Ser Gly Gln Pro His Met Glu Gln Val Pro Glu	
	565 570 575	
15	gcc cag ccc ctt ggg gac ttg ccc atc ctg gaa gtg gag gag atg gag	1776
	Ala Gln Pro Leu Gly Asp Leu Pro Ile Leu Glu Val Glu Glu Met Glu	
	580 585 590	
20	ccc ccg ccg gtt atg gag tcc tcc cag ccc gcc cag gcc acc gcc ccg	1824
	Pro Pro Pro Val Met Glu Ser Ser Gln Pro Ala Gln Ala Thr Ala Pro	
	595 600 605	
25	ctt gac tct ggg tat gag aag cac ttc ctg ccc aca cct gag gag ctg	1872
	Leu Asp Ser Gly Tyr Glu Lys His Phe Leu Pro Thr Pro Glu Glu Leu	
	610 615 620	
30	ggc ctt ctg ggg ccc ccc agg cca cag gtt ctg gcc tga	1911
	Gly Leu Leu Gly Pro Pro Arg Pro Gln Val Leu Ala	
	625 630 635	
35	MRGGRGAPFW LWPLPKLALL PLLWVLFQRT RPQGSAGPLQ CYGVGPLGDL NCSWEPLGDL	
	GAPSELHLQS QKYRSNKTQT VAVAAGRSWV AIPREQLTMS DKLLVWG.KA GQPLWPPVVFV	
	NLETQMKPNA PRLGPDVDFS EDDPLEATVH WAPPTWPSHK VLICQFHYRR CQEAATLLE	
	PELKTIPLTP VEIQDLELAT GYKVYGRCRM EKEEDLWGEW SPILSFQTPP SAPKDVWVSG	
	NLCGTPGGEE PLLLWKAPGP CVQVSYKVWF WVGGRELSPE GITCCCSLIP SGAEWARVSA	
	VNATSWEPLT NLSLVCLDSA SAPRSVAVSS IAGSTELLVT WQPGPGEPLH HVMWARDGD	
40	PLEKLNWVRL PPGNLSALLP GNFTVGVPIR ITVTAVSASG LASASSVWGF REELAPLVGP	
	TLWRLQDAPP GTPAIWAGEV PRHQLRGHLT HYTLCAQSGT SPSVCMNVSG NTQSVTLPLD	
	PWGPCELWVT ASTIAGQGPP GPILRLHLPD NTLRWKVLPG ILFLWGLFLL GCGLSLATSG	
	RCYHLRHKVL PRWVWEKVPD PANSSSGQPH MEQVPEAQPL GDLPILEVEE MEPPPVMESS	
	QPAQATAPLD SGYEKHFLLPT PEELGLLGPP RPQVLA	
	supplementary partial "upstream" rodent, e.g., mouse, DCRP1	
	sequences (SEQ ID NO: 14 and 15):	
45	ggt aag ccc caa gcc tgg tgg tgt cac ttg tcc ctg gga gcc atg aac	48
	Gly Lys Pro Gln Ala Trp Trp Cys His Leu Ser Leu Gly Ala Met Asn	
	1 5 10 15	
50	cgg ctc ggg ttt gca cgc ctc acg ccg ttg gag ctt ctg ctg tcg ctg	96
	Arg Leu Gly Phe Ala Arg Leu Thr Pro Leu Glu Leu Leu Ser Leu	
	20 25 30	
55	atg tcg ctg ctg ctc ggg acg cgg ccc cac ggc agt cca ggc cca ctg	144
	Met Ser Leu Leu Leu Gly Thr Arg Pro His Gly Ser Pro Gly Pro Leu	
	35 40 45	
	cag tgc tac agc gtc ggt ccc ctg gga atc ctg aac tgc tcc tgg gaa	192
	Gln Cys Tyr Ser Val Gly Pro Leu Gly Ile Leu Asn Cys Ser Trp Glu	
	50 55 60	

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      cct ttg ggc gac ctg gag act cca cct gtg ctg tat cac cag agt cag   240
      Pro Leu Gly Asp Leu Glu Thr Pro Pro Val Leu Tyr His Gln Ser Gln
      65                               70                               75                               80
5    aaa tac cat ccc aat aga gtc tgg gag gtg aag gtg cct tcc aaa cag   288
      Lys Tyr His Pro Asn Arg Val Trp Glu Val Lys Val Pro Ser Lys Gln
                               85                               90                               95
10   agt tgg gtg acc att ccc cgg gaa cag ttc acc atg gct gac aaa ctc   336
      Ser Trp Val Thr Ile Pro Arg Glu Gln Phe Thr Met Ala Asp Lys Leu
                               100                               105                               110
15   ctc atc tgg ggg aca caa aag gga cgg cct ctg tgg tcc tct gtc tct   384
      Leu Ile Trp Gly Thr Gln Lys Gly Arg Pro Leu Trp Ser Ser Val Ser
      115                               120                               125
20   gtg aac ctg gag acc caa atg aag cca gac aca cct cag atc ttc tct   432
      Val Asn Leu Glu Thr Gln Met Lys Pro Asp Thr Pro Gln Ile Phe Ser
      130                               135                               140
      caa gtg gat att tct gan   450
      Gln Val Asp Ile Ser Xaa
      145                               150

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25 Table 2: Comparison of rodent, e.g., mouse, and primate, e.g., human, DCRS1:

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30   mDCRS1  -----MNRLGXARLTPLELLLSLMSLLLGTRPHGSPGPLQCYSVGPLGILNCSWEPLGDL
      hDCRS1  MRGGRGAPFWLWPLPKLALLPLLWVLFQRTTRPQGSAGPLQCYGVGPLGDLNCSWEPLGDL
              :      * . * * * * * :   ***:***.*****.*****
35   mDCRS1  ETPPVLYHQSQKYHPNRVWEVKVPSKQSWVTIPREQFTMADKLLIWGTQKGRPLWSSVSV
      hDCRS1  GAPSELHLQSQKYRSNKTQTVAVAAGRSWVAIPREQLTMSDKLLVWGKAGQPLWPPVFV
              :*. *: * * *:.*:.. * *: :****:****:****:****:****:*.****:.*
40   mDCRS1  NLETQMKPDTPQIFSQVDIS-----
      hDCRS1  NLETQMKPNAPRLGPDVDFSEDDPLEATVHWAPPTWPSHKVLICQFHYRRCQEAAWTLLE
              * *****:.*:.. :****:
45   mDCRS1  -----
      hDCRS1  PELKTIPLTPVEIQDLELATGYKVYGRCRMKEEDLWGEWSPILSFQTPPSAPKDVWVSG
50   mDCRS1  -----
      hDCRS1  NLCGTPGGEEPLLLWKAPGPCVQVSYKVWFWVGGRELSPEGITCCCSLIPSGAEWARVSA
55   mDCRS1  -----
      hDCRS1  VNATSWEPLTNLSLVCLDSASAPRSVAVSSIAGSTELLVTWQPGPGEPLEHVMDWARDGD
60   mDCRS1  -----KGGVPYRITVTAVYSGGLAAAPSVWGFREELVPLAGP
      hDCRS1  PLEKLNWVRLPPGNLSALLPGNFTVGVPIRITVTAVSASGLASASSVWGFREELAPLVGP
              ***** . ***.***** ** **

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mDCRS1 AVWRLPDDPPGTPVVAWGEVPRHQLRGQATHYTFCIQSRGLSTVCRNVSSQTQTATLPNL  
hDCRS1 TLWRLQDAPPGTPAIAWGEVPRHQLRGHLTHYTLCAQSGTSPSVCNMVSGNTQSVTLPLD  
..\*\*\* \* \*\*\*\*\* .\*\*\*\*\*. \*\*\*\*\* \* \* . \* \* \* \* . \* \* . \* \* \*

5 mDCRS1 HSGSFKLWVTVSTVAGQGGPPGPDLSLHLPDNRIRWKALPWFLSLWGLLLMGCGLSLASTR  
hDCRS1 PWGPCELWVTASTIAGQGGPPGPIRLHLPDNTLRWKVLPGLFLWGLFLLGCGLSLATS-  
\* \* \* \* \* . \* \* \* \* \* \* \* \* \* \* . \* \* \* \* \* \* \* \* \* \* . \* \* \* \* \*

10 mDCRS1 CLQARCLHWRHKLLPQWIWERVDPANSSGQPYIKEVSLPQPPKDGPILEVEEVELQPV  
hDCRS1 ---GRCYHLRHKVLPWVWEKVPDPANSSSGQPHMEQVPEAQPLGDLPILEVEEMEPPPV  
\* \* \* \* \* . \* \* \* \* \* . \* \* \* \* \* \* \* \* \* \* . \* \* \* \* \* \* \* \* \* \* . \* \* \*

15 mDCRS1 VESPK---ASAPIYSGYEKHFLLPTPEELGLLV  
hDCRS1 MESSQPAQATAPLDSGYEKHFLLPTPEELGLLGPPRPQVLA  
. \* \* . \* \* . \* \* \* \* \* \* \* \* \* \* \*

20 Table 3: Alignment of various cytokine receptor subunits. Human  
gp130 sequence (hgp130) is SEQ ID NO: 5 (see GenBank M57230).  
Human G-CSF Receptor subunit alpha (hGCSFRa) is SEQ ID NO: 6 (see  
GenBank X55721). Human IL-12 Receptor subunit beta (hIL12Rb) is  
25 SEQ ID NO: 7 (see GenBank U64198). Consensus domain boundaries are  
described in the text.

30 mIL30Rb -----MNRLGXARLTPELELLSLMSLLLGTR-----  
hIL30Rb -----MRGGRGAPFWLWPLPKLALLPLLWVLFQTR-----  
human\_GCSF -----MARLGNCSTWAALIILLPGSLEECGHISVSAPIVHLGDPIT  
human\_gp13 MLTLQTWVQALFIFLTTESTGELLDP-----CGYISPESPVVQLHSNFT  
human\_IL12 MAHTFRGCSLAFMFIITWLLIKAKIDACK--RGDVTVKPSHVILLGSTVN

35 :

40 mIL30Rb -----  
hIL30Rb -----  
human\_GCSF ASCIHK--QNCSHLDPEPQ--ILWRLGAELQPGRQQRSLSDGTQESIITL  
human\_gp13 AVCVLK--EKCMDYFHVNYANYIVWKTNHFTIPKE-QYTIINRTASSVTFT  
human\_IL12 ITCSLKPRQGCFFHYSRRNK-LILYKFDRRINFHHGHSLSNSQVTGLPLG--

45 :

45 mIL30Rb -----PHGSPGPLQCYSVGPLGI  
hIL30Rb -----PQGSAGPLQCYGVGPLGD  
human\_GCSF PHLNHTQAFLSCCLNWGNSLQILDQVELRAGYPPAIPHNLSCLMNLTSS  
human\_gp13 DIASLNIQLTCNLTFGQLEQNVYGITIIISGLPPEKPKNLSCIVNEGK-K  
human\_IL12 -----TTLFVCKLACINSDEIQICGAEIFVGVAPEQPQNLSIQKGEQGT

50 . \* \*

55 mIL30Rb LNCWEPLGDLETPPVLYHQSQKYHPN-----RVWEVKVPS-KQSWVTIP  
hIL30Rb LNCWEPLGDLGAPSELHLQXQKYRSN-----KTQTVAVA--GRSWVAIP  
human\_GCSF LICQWEPGPETHLPTSFTLKSFKSRGNCQTQGDSILDCVPKDGQSHCCIP  
human\_gp13 MRCEWDGGRETHLETNFTLKS-EWATH-----KFADCKAKRDTPTSCTVD  
human\_IL12 VACTWERGRDTHLYTEYTLQL-SGPKN---LTWQKQCKDIYCDYLDGFIN  
: \* \* : : : : :

5	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	REQFTMADKLLIWGTQK---GRPLWSSSVNLETQMKPDTQPQIFSQVDIS REQLTMSDKLLVWGTKA---GQPLWPPVFVNLETQMKPNAPRLGPDVDFS RKHLLLYQNMGIWVQAENALGTSMSQPCLDPMVVKLEPPMLRTMDPSP YS-TVYFVNIEVWVEAENALGKVTSDHINFDPVYKVKPNPPHNLVSVINSE LTPESPESNFTAKVTAVNSLGSSSSLPSTFTFLDIVRPLPPWDIRIKFQK :: * :: *
10	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- EDDPLEA---TVHWAPPTWPSHKVLICQF-HYRRCQEAAWTLLEPELKTI EAAPPOAGCLQLCWEPWQPLHINQKCELRHKPQGEASWALVGPLP--L ELSSILK---LTWTNPSIKSVIILKYNI-QYRTKDASTWSQIPPEDTAS ASVSRCT---LYWRDE----GLVLLNRLRYRPSNSRLWNMNVTK---
15		
20	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- PLTPVEIQDLELATGYKVYGRCRMEKEEDLWGEWSPILSFQTPPSAP--- EALQYELCGLLPATAYTLQIRCIRWPLPGHWSWSPSLELRRTTERAPTVR TRSSFTVQDLKPFTYVFRIRCMKEDGKGYWSDWSEEASGITYEDRPSKA AKGRHDLDDLKPFTYEFQISSKLHLYKGSWSDWSESLRAQTPEEPTGM
25	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- KDVWVSG-----NLCGTPGGEEPLLLWKAPGPCVQVSYKVWFWVG---G LDTWWRQR---QLDPRTVQLFWKPVPLEEDSG-RIQGYVVSWRPSGQ---A PSFWYKIDPSHTQGYRTVQLVWKTLPPEFANGKILDYEVTLTRWKS---H LDVWYMKR-HIDYSRQQISLFWKNLSVSEARGKILHYQVTLQELTGKAM
30		
35	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- RELSPEGITCCCSLIPSGAEWARVSAVNATSWEPLTNLSLVCLDSASAPR GAILPLCNTTELSCFHLPSAQEVALVAYNSAGTSRPTPVVFSESRGPA LQNYTVNATKLTVNLTNDRYLATLTVRNLVGKSDAAVLTI PACDFQATHP TONITGHTSWTTVIPRTGNWAVAVSAANSKGSSLPTRINIMNLCEAGLLA
40	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- SVAVSSIAGS-TELLVTWQPGPGEP---LEHVMDWARDGD-PLEKLN--W LTRLHAMARDPHSLWVGWEPNPWP---QGYVIEWGLGPP-SASNSNKTW VMDLKAFPKD-NMLWVEWTPPRESV---KKYILEWCVLSD-KAPCIT-DW PRQVSANSEGMDNILVTWQPPRKDPSAVQYVVEWRELHPGGDTQVPLNW
45		
50	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- KGGVPYRITVTAVYSGGLAAAPSVWGFFREELVP VRLPPG-NLSALLPGNFTVGVYRITVTAVSASGLASASSVWGFFREELAP RMEQNGRATGFLLENIRPFQLYEIIIVTPLYQDTMGPSQHVYAYSQEMAP QQE-DGTVHRTYLRGNLAESKCYLITVTPVYADGPGSPESIKAYLKQAPP LRS-RPYNVSALISENIKSYICYEIRVYALSGD-QGGCSSILGNSKHKAP
55		
60	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	LAGPAVWRLPDDPPGTPVVAWGEVPRHQLRGQATHYTFCIQ----SRGLS LVGPTLWRLQDAPPGTPAIAWGEVPRHQLRGHLTHYTLCAQ----SGTSP SHAP-ELHLKHIGKTWAQLEWVPEPPELGKSPLTHYTIFWT----NAQNQ SKGP-TVRTKKVGKNEAVLEWDQLPVDVQNGFIRNYTIFYR----TIIGN LSGP-HINAITEEKGSILISWNSIPVQEQMGCLLHYRIYWKERDSNSQPQ

5	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	TVCRNVSSQTQTATLPNLHSGSFKLWTVSTVAGQGPPGPDLSLHLPDNR SVC MNVSGNTQSVTL PDL PWGPCELWVTASTIAGQGPPGPILRLHLPDNT SFSAILNASSRGFVLHGL--EPASLYHIHLMAASQAGATNSTVLTLMTLT ETAVNVDSSHTYTLSSL--TSDTLYMVRMAAYTDEGGKDGPEFTFTPK LCEIPYRVSQNSHPINSL--QPRVTYVLWMTALTAAGESSHGNEREFCLQ
10	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	IRWKALPWFLSLWGLLLMGCGLSLASTRCLQARCLHWRHKLLPQWIWER- LRWKVLPGLFLWGLFLLGCGLSLATS---GRCYHLRHKVLPRVWWEK- PEGSELHIILGLFGLLLLLTCLCGTAW----LCCSPNR----KNPLWPS- FAQGEIEAIVVPVCLAFLLTTLG-----VLFCFNKR-DLIKHHIWP- N-GKANWMAFVAPSICIAIIMVGIFSTHY----FQKVFVLLAALRPQWCSR
15	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	-VPDPANSNSG-----QPYIKEVS----LPQPPKDG-----ILEVEEVE -VPDPANSSSG-----QPHMEQVP----EAQPLGDL-----ILEVEE-- -VPDPAHSSLGSWVPTIMEEDAFQLPG--LGTPPITKLT--VLEEDE-- -VPDPSKSHIAQWSPHTPPRHNFNSKDQMYSDGNFTDVS---VVEIEAND EIPDPANSTCAKKYPIAEKTLPLDR-LLIDWPTPEDPEPLVISEVLHQ
25	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	LQPV-----PVVESPK---AS----- MEPP-----PVMESSQPAQAT----- KKPVPWESHNSSET--CGLPTLVQTYVLQGDPRAVSTQPQSQSG---TS KKFPEDLKSLDLFKKEKINTEGHSSGIGSSCMSSSRPSISSDENESS VTPVFRHPPCSNWPQREKGIQGHQASEKDMMSASSPPPPRALQAE---S
30	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	-----APIYSG-----YEKHFLLPTP----- -----APLDSG-----YEKHFLLPTP----- DQVLYGQLLGSPTSPGPGHYLRCDSTQPLLAGLTPSPKSYENLW----FQ QNTSSTVQYSTVHSGYRQVPSVQVFSRSESTQPLLDSEERPEDLQLVD RQLVDLYKVLESRGSDPKPENPACPWTVLPAGDLPTHGYP-----SN
40	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	-EELGLLV----- -EELGLLGPPRP-QVLA----- ASPLGTLVTPAP-SQEDDCVFG---P-LLNFPLLQGI RVHGMEALGSF-- HVDGGDGILPRQYFKQNC SQHESSPDISHFERSKQVSSVNEEDFVRLKQ IDDLPSHEAPLADSLEELPQHISLSVFPSSSLHPLTFSCGDKLTL DQLK
45	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- ----- ----- ----- QISDHISQSCGSGQM KMFQEVSAADAFGPGTEGQVERFETVGMEAATDEG MRCDSLML-----
50	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- ----- ----- ----- -----
55	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- ----- ----- ----- MPKSYLPQT V RQGGYMPQ -----
60	mIL30Rb hIL30Rb human_GCSF human_gp13 human_IL12	----- ----- ----- ----- -----

Table 4: Sequences of mammalian DNAX Soluble Receptor Subunit 1 (DSRS1). Primate, e.g., human, nucleotide and polypeptide sequences (SEQ ID NO: 8 and 9; note WSEWS motif at 327-331):

5	atg ccc gcc ggc cgc cgg ggc ccc gcc gcc caa tcc gcg cgg cgg ccg	48
	Met Pro Ala Gly Arg Arg Gly Pro Ala Ala Gln Ser Ala Arg Arg Pro	
	1 5 10 15	
10	ccg ccg ttg ctg ccc ctg ctg ctg ctg ctc tgc gtc ctc ggg gcg ccg	96
	Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu Cys Val Leu Gly Ala Pro	
	20 25 30	
15	cga gcc gga tca gga gcc cac aca gct gtg atc agt ccc cag gat ccc	144
	Arg Ala Gly Ser Gly Ala His Thr Ala Val Ile Ser Pro Gln Asp Pro	
	35 40 45	
20	acg ctt ctc atc ggc tcc tcc ctg ctg gcc acc tgc tca gtg cac gga	192
	Thr Leu Leu Ile Gly Ser Ser Leu Leu Ala Thr Cys Ser Val His Gly	
	50 55 60	
25	gac cca cca gga gcc acc gcc gag ggc ctc tac tgg acc ctc aac ggg	240
	Asp Pro Pro Gly Ala Thr Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly	
	65 70 75 80	
30	cgc cgc ctg ccc cct gag ctc tcc cgt gta ctc aac gcc tcc acc ttg	288
	Arg Arg Leu Pro Pro Glu Leu Ser Arg Val Leu Asn Ala Ser Thr Leu	
	85 90 95	
35	gct ctg gcc ctg gcc aac ctc aat ggg tcc agg cag cgg tcc ggg gac	336
	Ala Leu Ala Ala Asn Leu Asn Gly Ser Arg Gln Arg Ser Gly Asp	
	100 105 110	
40	aac ctc gtg tgc cac gcc cgt gac ggc agc atc ctg gct ggc tcc tgc	384
	Asn Leu Val Cys His Ala Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys	
	115 120 125	
45	ctc tat gtt ggc ctg ccc cca gag aaa ccc gtc aac atc agc tgc tgg	432
	Leu Tyr Val Gly Leu Pro Pro Glu Lys Pro Val Asn Ile Ser Cys Trp	
	130 135 140	
50	tcc aag aac atg aag gac ttg acc tgc cgc tgg acg cca ggg gcc cac	480
	Ser Lys Asn Met Lys Asp Leu Thr Cys Arg Trp Thr Pro Gly Ala His	
	145 150 155 160	
55	ggg gag acc ttc ctc cac acc aac tac tcc ctc aag tac aag ctt agg	528
	Gly Glu Thr Phe Leu His Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg	
	165 170 175	
60	tgg tat ggc cag gac aac aca tgt gag gag tac cac aca gtg ggg ccc	576
	Trp Tyr Gly Gln Asp Asn Thr Cys Glu Glu Tyr His Thr Val Gly Pro	
	180 185 190	
65	cac tcc tgc cac atc ccc aag gac ctg gct ctc ttt acg ccc tat gag	624
	His Ser Cys His Ile Pro Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu	
	195 200 205	
70	atc tgg gtg gag gcc acc aac cgc ctg ggc tct gcc cgc tcc gat gta	672
	Ile Trp Val Glu Ala Thr Asn Arg Leu Gly Ser Ala Arg Ser Asp Val	
	210 215 220	

	ctc acg ctg gat atc ctg gat gtg gtg acc acg gac ccc ccg ccc gac	720
	Leu Thr Leu Asp Ile Leu Asp Val Val Thr Thr Asp Pro Pro Pro Asp	
	225 230 235 240	
5	gtg cac gtg agc cgc gtc ggg ggc ctg gag gac cag ctg agc gtg cgc	768
	Val His Val Ser Arg Val Gly Gly Leu Glu Asp Gln Leu Ser Val Arg	
	245 250 255	
10	tgg gtg tcg cca ccc gcc ctc aag gat ttc ctc ttt caa gcc aaa tac	816
	Trp Val Ser Pro Pro Ala Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr	
	260 265 270	
15	cag atc cgc tac cga gtg gag gac agt gtg gac tgg aag gtg gtg gac	864
	Gln Ile Arg Tyr Arg Val Glu Asp Ser Val Asp Trp Lys Val Val Asp	
	275 280 285	
20	gat gtg agc aac cag acc tcc tgc cgc ctg gcc ggc ctg aaa ccc ggc	912
	Asp Val Ser Asn Gln Thr Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly	
	290 295 300	
	acc gtg tac ttc gtg caa gtg cgc tgc aac ccc ttt ggc atc tat ggc	960
	Thr Val Tyr Phe Val Gln Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly	
	305 310 315 320	
25	tcc aag aaa gcc ggg atc tgg agt gag tgg agc cac ccc aca gcc gcc	1008
	Ser Lys Lys Ala Gly Ile Trp Ser Glu Trp Ser His Pro Thr Ala Ala	
	325 330 335	
30	tcc act ccc cgc agt gag cgc ccg ggc ccg ggc ggc ggg gcg tgc gaa	1056
	Ser Thr Pro Arg Ser Glu Arg Pro Gly Pro Gly Gly Ala Cys Glu	
	340 345 350	
35	ccg cgg ggc gga gag ccg agc tcg ggg ccg gtg cgg cgc gag ctc aag	1104
	Pro Arg Gly Gly Glu Pro Ser Ser Gly Pro Val Arg Arg Glu Leu Lys	
	355 360 365	
40	cag ttc ctg ggc tgg ctc aag aag cac gcg tac tgc tcc aac ctc agc	1152
	Gln Phe Leu Gly Trp Leu Lys Lys His Ala Tyr Cys Ser Asn Leu Ser	
	370 375 380	
	ttc cgc ctc tac gac cag tgg cga gcc tgg atg cag aag tcg cac aag	1200
	Phe Arg Leu Tyr Asp Gln Trp Arg Ala Trp Met Gln Lys Ser His Lys	
	385 390 395 400	
45	acc cgc aac cag gtc ctg cca gat aag ctg tag	1233
	Thr Arg Asn Gln Val Leu Pro Asp Lys Leu	
	405 410	
50	MPAGRRGPAA QSARRPPPLL PLLLLLCVLG APRAGSGAHT AVISPQDPTL LIGSSLLATC	
	SVHGDPPGAT AEGLYWTLNG RRLPPELSRV LNA STLALAL ANLNGSRQRS GDNLVCHARD	
	GSILAGSCLY VGLPPEKPVN ISCWSKNMKD LTCRWTPGAH GETFLHTNYS LKYKLRWYGQ	
	DNTCEEYHTV GPHSCHIPKD LALFTPYEIW VEATNRLGSA RSDVLTL DIL DVVTTDPPPD	
	VHVS RVGGLE DQLSVRWVSP PALKDFLFQA KYQIRYRVED SVDWKVVDDV SNQTSCLAG	
55	LKPGTVYFVQ VRCNPFGIYG SKKAGIWSEW SHPTAASTPR SERPGPGGGA CEPRGGEPS	
	GPVRRELKQF LGWLKKHAYC SNLSFRLYDQ WRAWMQKSHK TRNQVLPDKL	

Partial rodent, e.g., mouse, nucleotide and polypeptide sequences,  
note WSEWS motif at 321-325 (SEQ ID NO: 10 and 11):

5	ccc tca cta aag gga ata agc ttg cgg ccg ctg tcc tcg ctg tgg tcg	48
	Pro Ser Leu Lys Gly Ile Ser Leu Arg Pro Leu Ser Ser Leu Trp Ser	
	1 5 10 15	
10	cct ctg ttg ctc tgt gtc ctc ggg gtg cct cgg ggc gga tcg gga gcc	96
	Pro Leu Leu Leu Cys Val Leu Gly Val Pro Arg Gly Gly Ser Gly Ala	
	20 25 30	
15	cac aca gct gta atc agc ccc cag gac ccc acc ctt ctc atc ggc tcc	144
	His Thr Ala Val Ile Ser Pro Gln Asp Pro Thr Leu Leu Ile Gly Ser	
	35 40 45	
20	tcc ctg caa gct acc tgc tct ata cat gga gac aca cct ggg gcc acc	192
	Ser Leu Gln Ala Thr Cys Ser Ile His Gly Asp Thr Pro Gly Ala Thr	
	50 55 60	
25	gct gag ggg ctc tac tgg acc ctc aat ggt cgc cgc ctg ccc tct gag	240
	Ala Glu Gly Leu Tyr Trp Thr Leu Asn Gly Arg Arg Leu Pro Ser Glu	
	65 70 75 80	
30	ctg tcc cgc ctc ctt aac acc tcc acc ctg gcc ctg gcc ctg gct aac	288
	Leu Ser Arg Leu Leu Asn Thr Ser Thr Leu Ala Leu Ala Leu Ala Asn	
	85 90 95	
35	ctt aat ggg tcc agg cag cag tca gga gac aat ctg gtg tgt cac gcc	336
	Leu Asn Gly Ser Arg Gln Gln Ser Gly Asp Asn Leu Val Cys His Ala	
	100 105 110	
40	cga gat ggc agc att ctg gct ggc tcc tgc ctc tat gtt ggc ttg ccc	384
	Arg Asp Gly Ser Ile Leu Ala Gly Ser Cys Leu Tyr Val Gly Leu Pro	
	115 120 125	
45	cct gag aag cct ttt aac atc agc tgc tgg tcc cgg aac atg aag gat	432
	Pro Glu Lys Pro Phe Asn Ile Ser Cys Trp Ser Arg Asn Met Lys Asp	
	130 135 140	
50	ctc acg tgc cgc tgg aca ccg ggt gca cac ggg gag aca ttc tta cat	480
	Leu Thr Cys Arg Trp Thr Pro Gly Ala His Gly Glu Thr Phe Leu His	
	145 150 155 160	
55	acc aac tac tcc ctc aag tac aag ctg agg tgg tac ggt cag gat aac	528
	Thr Asn Tyr Ser Leu Lys Tyr Lys Leu Arg Trp Tyr Gly Gln Asp Asn	
	165 170 175	
60	aca tgt gag gag tac cac act gtg ggc cct cac tca tgc cat atc ccc	576
	Thr Cys Glu Glu Tyr His Thr Val Gly Pro His Ser Cys His Ile Pro	
	180 185 190	
65	aag gac ctg gcc ctc ttc act ccc tat gag atc tgg gtg gaa gcc acc	624
	Lys Asp Leu Ala Leu Phe Thr Pro Tyr Glu Ile Trp Val Glu Ala Thr	
	195 200 205	
70	aat cgc cta ggc tca gca aga tct gat gtc ctc aca ctg gat gtc ctg	672
	Asn Arg Leu Gly Ser Ala Arg Ser Asp Val Leu Thr Leu Asp Val Leu	
	210 215 220	
75	gac gtg gtg acc acg gac ccc cca ccc gac gtg cac gtg agc cgc gtt	720
	Asp Val Val Thr Thr Asp Pro Pro Pro Asp Val His Val Ser Arg Val	
	225 230 235 240	

	ggg ggc ctg gag gac cag ctg agt gtg cgc tgg gtc tca cca cca gct	768
	Gly Gly Leu Glu Asp Gln Leu Ser Val Arg Trp Val Ser Pro Pro Ala	
	245 250 255	
5	ctc aag gat ttc ctc ttc caa gcc aag tac cag atc cgc tac cgc gtg	816
	Leu Lys Asp Phe Leu Phe Gln Ala Lys Tyr Gln Ile Arg Tyr Arg Val	
	260 265 270	
10	gag gac agc gtg gac tgg aag gtg gtg gat gac gtc agc aac cag acc	864
	Glu Asp Ser Val Asp Trp Lys Val Val Asp Asp Val Ser Asn Gln Thr	
	275 280 285	
15	tcc tgc cgt ctc gcg ggc ctg aag ccc ggc acc gtt tac ttc gtc caa	912
	Ser Cys Arg Leu Ala Gly Leu Lys Pro Gly Thr Val Tyr Phe Val Gln	
	290 295 300	
20	gtg cgt tgt aac cca ttc ggg atc tat ggg tgc aaa aag gcg gga atc	960
	Val Arg Cys Asn Pro Phe Gly Ile Tyr Gly Ser Lys Lys Ala Gly Ile	
	305 310 315 320	
	tgg agc gag tgg agc cac ccc acc gct gcc tcc acc cct cga agt gag	1008
	Trp Ser Glu Trp Ser His Pro Thr Ala Ala Ser Thr Pro Arg Ser Glu	
	325 330 335	
25	cgc ccg ggc ccg ggc ggc ggg gtg tgc gag ccg cgg ggc ggc gag ccc	1056
	Arg Pro Gly Pro Gly Gly Gly Val Cys Glu Pro Arg Gly Gly Glu Pro	
	340 345 350	
30	agc tgc ggc ccg gtg cgg cgc gag ctc aag cag ttc ctc ggc tgg ctc	1104
	Ser Ser Gly Pro Val Arg Arg Glu Leu Lys Gln Phe Leu Gly Trp Leu	
	355 360 365	
35	aag aag cac gca tac tgc tgc aac ctt agt ttc cgc ctg tac gac cag	1152
	Lys Lys His Ala Tyr Cys Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln	
	370 375 380	
40	tgg cgt gct tgg atg cag aag tca cac aag acc cga aac cag gac gag	1200
	Trp Arg Ala Trp Met Gln Lys Ser His Lys Thr Arg Asn Gln Asp Glu	
	385 390 395 400	
	ggg atc ctg ccc tgc ggc aga cgg ggt gcg gcg aga ggt cct gcc ggc	1248
	Gly Ile Leu Pro Ser Gly Arg Arg Gly Ala Ala Arg Gly Pro Ala Gly	
	405 410 415	
45	taaactctaa ggataggcca tctctctgct gggtcagacc tggagggtca cctgaattgg	1308
	agcccctctg taccatctgg gcaacaaaga aacctaccag aggctggggc acaatgagct	1368
50	cccacaacca cagctttggt ccacatgatg gtcacacttg gatatacccc agtgtgggta	1428
	gggttgggggt attgcagggc ctcccaagag tttttttaaa taaataaagg agttgttcag	1488
	gtcccgatgg naaaaaaaaa aaaaaaaaaa aaaaaa	1524

Table 5: Alignment of primate, e.g., human, and rodent, e.g., mouse, DRSR1 (SEQ ID NO: 9 and 11):

5	hDSRS1	MPAGRRGPAA	QSARRPPPLL	PLLLLLCVLG	APRAGSGAHT	AVISPODPTL											
	mDSRS1	.....	....RPLSSL	WSPLLLCVLG	VPRGGSGAHT	AVISPODPTL											
10	hDSRS1	LIGSSLLATC	SVHGDPPGAT	AEGLYWTLNG	RRLPPELSRV	LNASTLALAL											
	mDSRS1	LIGSSLQATC	SIHGDTPGAT	AEGLYWTLNG	RRLPSELSRL	LNTSTLALAL											
15	hDSRS1	ANLNGSRQRS	GDNLVCHARD	GSILAGSCLY	VGLPPEKPVN	ISCWSKNMKD											
	mDSRS1	ANLNGSRQOS	GDNLVCHARD	GSILAGSCLY	VGLPPEKPFN	ISCWSRNMKD											
20	hDSRS1	LTCRWTPGAH	GETFLHTNYS	LKYKLRWYQ	DNTCEEYHTV	GPHSCHIPKD											
	mDSRS1	LTCRWTPGAH	GETFLHTNYS	LKYKLRWYQ	DNTCEEYHTV	GPHSCHIPKD											
25	hDSRS1	LALFTPYEIW	VEATNRLGSA	RSDVLTLDIL	DVVTDDPPPD	VHVS RVGGLE											
	mDSRS1	LALFTPYEIW	VEATNRLGSA	RSDVLTLDVL	DVVTDDPPPD	VHVS RVGGLE											
30	hDSRS1	DQLSVRWVSP	PALKDFLFQA	KYQIRYRVED	SVDWKVVDDV	SNQTSCLAG											
	mDSRS1	DQLSVRWVSP	PALKDFLFQA	KYQIRYRVED	SVDWKVVDDV	SNQTSCLAG											
35	hDSRS1	LKPGTVYFVQ	VRCPNFGIYG	SKKAGIWSEW	SHPTAASTPR	SERPGPGGGA											
	mDSRS1	LKPGTVYFVQ	VRCPNFGIYG	SKKAGIWSEW	SHPTAASTPR	SERPGPGGGV											
40	hDSRS1	CEPRGGEPSS	GPVRRELKQF	LGWLKKHAYC	SNLSFRLYDQ	WRAWMQKSHK											
	mDSRS1	CEPRGGEPSS	GPVRRELKQF	LGWLKKHAYC	SNLSFRLYDQ	WRAWMQKSHK											
45	hDSRS1	TRNQ...VLP	DKL.....	..													
	mDSRS1	TRNQDEGILP	SGRRGAARGP	AG													
48	atg	ctg	ggg	agc	aga	gct	gta	atg	ctg	ctg	ttg	ctg	ctg	ccc	tgg	aca	
	Met	Leu	Gly	Ser	Arg	Ala	Val	Met	Leu	Leu	Leu	Leu	Leu	Pro	Trp	Thr	
		-20					-15							-10			
96	gct	cag	ggc	aga	gct	gtg	cct	ggg	ggc	agc	agc	cct	gcc	tgg	act	cag	
	Ala	Gln	Gly	Arg	Ala	Val	Pro	Gly	Gly	Ser	Ser	Pro	Ala	Trp	Thr	Gln	
		-5			-1	1				5					10		
144	tgc	cag	cag	ctt	tca	cag	aag	ctc	tgc	aca	ctg	gcc	tgg	agt	gca	cat	
	Cys	Gln	Gln	Leu	Ser	Gln	Lys	Leu	Cys	Thr	Leu	Ala	Trp	Ser	Ala	His	
				15					20					25			
192	cca	cta	gtg	gga	cac	atg	gat	cta	aga	gaa	gag	gga	gat	gaa	gag	act	
	Pro	Leu	Val	Gly	His	Met	Asp	Leu	Arg	Glu	Glu	Gly	Asp	Glu	Glu	Thr	
			30					35						40			

Table 6: Primate, e.g., human, IL-B30 nucleotide and polypeptide sequences. Predicted signal cleavage site indicated, but may actually be a residue or more to either side, depending upon the cell (SEQ ID NO: 16 and 17):



	aca aat gat gtt ccc cat atc cag tgt gga gat ggc tgt gac ccc caa	240
	Thr Asn Asp Val Pro His Ile Gln Cys Gly Asp Gly Cys Asp Pro Gln	
	45 50 55	
5	gga ctc agg gac aac agt cag ttc tgc ttg caa agg atc cac cag ggt	288
	Gly Leu Arg Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile His Gln Gly	
	60 65 70 75	
10	ctg att ttt tat gag aag ctg cta gga tgc gat att ttc aca ggg gag	336
	Leu Ile Phe Tyr Glu Lys Leu Leu Gly Ser Asp Ile Phe Thr Gly Glu	
	80 85 90	
15	cct tct ctg ctc cct gat agc cct gtg gcg cag ctt cat gcc tcc cta	384
	Pro Ser Leu Leu Pro Asp Ser Pro Val Ala Gln Leu His Ala Ser Leu	
	95 100 105	
20	ctg ggc ctc agc caa ctc ctg cag cct gag ggt cac cac tgg gag act	432
	Leu Gly Leu Ser Gln Leu Leu Gln Pro Glu Gly His His Trp Glu Thr	
	110 115 120	
25	cag cag att cca agc ctc agt ccc agc cag cca tgg cag cgt ctc ctt	480
	Gln Gln Ile Pro Ser Leu Ser Pro Ser Gln Pro Trp Gln Arg Leu Leu	
	125 130 135	
30	ctc cgc ttc aaa atc ctt cgc agc ctc cag gcc ttt gtg gct gta gcc	528
	Leu Arg Phe Lys Ile Leu Arg Ser Leu Gln Ala Phe Val Ala Val Ala	
	140 145 150 155	
35	gcc cgg gtc ttt gcc cat gga gca gca acc ctg agt ccc taa	570
	Ala Arg Val Phe Ala His Gly Ala Ala Thr Leu Ser Pro	
	160 165	
40	MLGSRAVMLL LLLPWTAGQR AVPGGSSPAW TQCQQLSQKL CTLAWSAHPL VGHMDLREEG DEETTNDVPH IQCGDGCDFQ GLRDNSQFCL QRIHQGLIFY EKLLGSDIFT GEPSLLPDSP VAQLHASLLG LSQLLQPEGH HWETQQIPSL SPSQPWQRL LRFKILRSIQ AFVAVARVF AHGAATLSP	
45	cgcttagaag tcggactaca gagtagact cagaacaaa ggaggtggat aggggggtcca	60
	caggcctggt gcagatcaca gagccagcca gatctgagaa gcagggaaca ag atg ctg	118
		Met Leu
		-20
50	gat tgc aga gca gta ata atg cta tgg ctg ttg ccc tgg gtc act cag	166
	Asp Cys Arg Ala Val Ile Met Leu Trp Leu Leu Pro Trp Val Thr Gln	
	-15 -10 -5	
55	ggc ctg gct gtg cct agg agt agc agt cct gac tgg gct cag tgc cag	214
	Gly Leu Ala Val Pro Arg Ser Ser Ser Pro Asp Trp Ala Gln Cys Gln	
	-1 1 5 10	
60	cag ctc tct cgg aat ctc tgc atg cta gcc tgg aac gca cat gca cca	262
	Gln Leu Ser Arg Asn Leu Cys Met Leu Ala Trp Asn Ala His Ala Pro	
	15 20 25	

	gcg gga cat atg aat cta cta aga gaa gaa gag gat gaa gag act aaa	310
	Ala Gly His Met Asn Leu Leu Arg Glu Glu Glu Asp Glu Glu Thr Lys	
	30 35 40 45	
5	aat aat gtg ccc cgt atc cag tgt gaa gat ggt tgt gac cca caa gga	358
	Asn Asn Val Pro Arg Ile Gln Cys Glu Asp Gly Cys Asp Pro Gln Gly	
	50 55 60	
10	ctc aag gac aac agc cag ttc tgc ttg caa agg atc cgc caa ggt ctg	406
	Leu Lys Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile Arg Gln Gly Leu	
	65 70 75	
15	gct ttt tat aag cac ctg ctt gac tct gac atc ttc aaa ggg gag cct	454
	Ala Phe Tyr Lys His Leu Leu Asp Ser Asp Ile Phe Lys Gly Glu Pro	
	80 85 90	
20	gct cta ctc cct gat agc ccc atg gag caa ctt cac acc tcc cta cta	502
	Ala Leu Leu Pro Asp Ser Pro Met Glu Gln Leu His Thr Ser Leu Leu	
	95 100 105	
	gga ctc agc caa ctc ctc cag cca gag gat cac ccc cgg gag acc caa	550
	Gly Leu Ser Gln Leu Leu Gln Pro Glu Asp His Pro Arg Glu Thr Gln	
	110 115 120 125	
25	cag atg ccc agc ctg agt tct agt cag cag tgg cag cgc ccc ctt ctc	598
	Gln Met Pro Ser Leu Ser Ser Ser Gln Gln Trp Gln Arg Pro Leu Leu	
	130 135 140	
30	cgt tcc aag atc ctt cga agc ctc cag gcc ttt ttg gcc ata gct gcc	646
	Arg Ser Lys Ile Leu Arg Ser Leu Gln Ala Phe Leu Ala Ile Ala Ala	
	145 150 155	
35	cgg gtc ttt gcc cac gga gca gca act ctg act gag ccc tta gtg cca	694
	Arg Val Phe Ala His Gly Ala Ala Thr Leu Thr Glu Pro Leu Val Pro	
	160 165 170	
40	aca gct taaggatgcc caggttccca tggctaccat gataagacta atctatcagc	750
	Thr Ala	
	175	
	ccagacatct accagttaat taaccattta ggacttggtgc tgttcttggtt tcgtttggtt	810
	tgcgtgaagg gcaaggacac cattattaaa gagaaaagaa acaaacccca gagcaggcag	870
45	ctggctagag aaaggagctg gagaagaaga ataaagtctc gagcccttgg ccttggaagc	930
	gggcaagcag ctgcgtggcc tgaggggaag ggggcggtgg catcgagaaa ctgtgagaaa	990
50	accagagca tcagaaaaag tgagcccagg ctttggccat tatctgtaag aaaaacaaga	1050
	aaaggggaac attatacttt cctgggtggc tcagggaaat gtgcagatgc acagtactcc	1110
	agacagcagc tctgtacctg cctgctctgt ccctcagttc taacagaatc tagtactaa	1170
55	gaactaacag gactaccaat acgaactgac aaa	1203
60	MLDCRAVIML WLLPWVTQGL AVPRSSSPDW AQCQQLSRNL CMLAWNAHAP AGHMNLLREE	
	EDEETKNNVP RIQCEDGCDP QGLKDNSQFC LQRIROGLAF YKHLSDIF KGEPALLPDS	
	PMEQLHTSLL GLSQLLQPED HPRETQQMPS LSSSQWQRP LLRSKILRSL QAFLAIAARV	
	FAHGAATLTE PLVPTA	

Partial polypeptide sequence of IL-B30 from pig (SEQ ID NO: 20):

```

5   Ser Cys Leu Gln Arg Ile His Gln Gly Leu Val Phe Tyr Glu Lys Leu
    1           5           10           15
10  Leu Gly Ser Asp Ile Phe Thr Gly Glu Pro Ser Leu His Pro Asp Gly
    20           25           30
    Ser Val Gly Gln Leu His Ala Ser Leu Leu Gly Leu Arg Gln Leu Leu
    35           40           45
    Gln Pro Glu Gly His His Trp Glu Thr Glu Gln Thr Pro Ser Pro Ser
    50           55           60
15  Pro Ser Gln Pro Trp Gln Arg Leu Leu Leu Arg Leu Lys Ile Leu Arg
    65           70           75           80
    Ser Leu Gln Ala Phe Val Ala Val Ala Ala Arg Val Phe Ala His Gly
    85           90           95
20  Ala Ala Thr Leu Ser Gln
    100

25  SCLQRIHQGLVIFYEKLLGSDIFTGEP SLHPDG SVGQLHASLLGLRQLLQPEGHHWETEQT P SPSPSQ
    PWQRL LRLKILRS LQAFVAVAA RVFAHGAATLSQ

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30 Table 2 shows comparison of the available sequences of primate and rodent embodiments of DCRS1. Table 3 shows the alignment of the DCRS1 with other cytokine receptor subunits. The DCRS1 shows particular similarity to the IL-12 receptor subunit beta, though it may be aligned with the gp130 (IL-6

35 receptor beta) and G-CSF receptor (alpha) subunits. The similarity to the IL-12 receptor subunit suggests that the functional receptor incorporating the DCRS1 may be similar to the IL-12 receptor. The IL-12 receptor alpha subunit is a soluble subunit. The DSRS1 is likely to be the corresponding

40 soluble subunit, which would initially interact with ligand, e.g., the IL-B30, and then form a functional complex with the DCRS1. See, e.g., Presky, et al. (1996) Proc. Nat'l Acad. Sci. USA 93:14002-14007. Alternatively, the soluble subunit may interact with the transmembrane receptor subunit, which

45 then could bind ligand.

Table 4 provides the nucleotide and polypeptide sequences of two species embodiments of a soluble receptor subunit designated DNAX Soluble Receptor Subunit 1 (DSRS1).

These align with and exhibit features in common with other cytokine receptor alpha type subunits. These subunits are believed to interact with the corresponding DCRS1 to form a functional receptor when the receptor ligand is present. Note  
5 that relatively close sequence similarity of the DCRS1 is with gp130, which is the beta subunit of the IL-6 receptor. Applicants believe that the ligand for the receptor is likely the ligand designated IL-B30, whose sequence is near to G-CSF and IL-6. See USSN 60/053,765, which is incorporated herein  
10 by reference.

Table 5 shows alignment of the DSRS1 from the primate and rodent species. Applicants believe that this soluble subunit forms a dimer, and binds to its dimerized ligand, which then combines with a beta type homo or heterodimer.  
15 Alternatively, the soluble subunit may bind to the transmembrane subunit(s), and then bind ligand.

Structural features of the human DCRS1, and similarly for the other receptors as aligned in Table 3, include characteristic Ig domains from about (SEQ ID NO: 2) val1 to  
20 pro133; fibronectin domains corresponding to the DCRS1 sequence from about gly134 to pro232, gly233 to gly306, and pro307 to lys403; a transmembrane segment from about val404 to gly427; and an intracellular domain from about arg428 to the carboxy terminus. Of particular interest is the WGEWS motif  
25 corresponding to residues trp104 to ser108. In many contexts, various variants and fragments will be equivalent to the described DSRS1.

As used herein, the term DCRS1 shall be used to describe a protein comprising the amino acid sequence  
30 shown in Table 1. In many cases, a substantial fragment thereof will be functionally or structurally equivalent, including, e.g., an extracellular or intracellular domain. The invention also includes a protein variation of the respective DCRS1 allele whose sequence is  
35 provided, e.g., a mutein or soluble extracellular construct. Typically, such agonists or antagonists will exhibit less than about 10% sequence differences, and thus will often have between 1- and 11-fold

substitutions, e.g., 2-, 3-, 5-, 7-fold, and others. It also encompasses allelic and other variants, e.g., natural polymorphic, of the protein described. Typically, it will bind to its corresponding biological  
5 ligand, perhaps in a dimerized state with an alpha receptor subunit, with high affinity, e.g., at least about 100 nM, usually better than about 30 nM, preferably better than about 10 nM, and more preferably at better than about 3 nM. The term shall also be used herein to  
10 refer to related naturally occurring forms, e.g., alleles, polymorphic variants, and metabolic variants of the mammalian protein. Preferred forms of the receptor complexes will bind the appropriate ligand with an affinity and selectivity appropriate for a ligand-  
15 receptor interaction.

This invention also encompasses combinations of proteins or peptides having substantial amino acid sequence identity with the amino acid sequence in Table 1. It will include sequence variants with relatively few  
20 substitutions, e.g., preferably less than about 3-5. Other embodiments include forms in association with an alpha subunit, e.g., a DSRS1, and/or with ligand, e.g., IL-B30.

A substantial polypeptide "fragment", or "segment",  
25 is a stretch of amino acid residues of at least about 8 amino acids, generally at least 10 amino acids, more generally at least 12 amino acids, often at least 14 amino acids, more often at least 16 amino acids, typically at least 18 amino acids, more typically at  
30 least 20 amino acids, usually at least 22 amino acids, more usually at least 24 amino acids, preferably at least 26 amino acids, more preferably at least 28 amino acids, and, in particularly preferred embodiments, at least about 30 or more amino acids. Sequences of segments of  
35 different proteins can be compared to one another over appropriate length stretches. In many situations, fragments may exhibit functional properties of the intact subunits, e.g., the extracellular domain of the

transmembrane receptor may retain the ligand binding features, and may be used to prepare a soluble receptor-like complex.

Amino acid sequence homology, or sequence identity, is determined by optimizing residue matches. In some comparisons, gaps may be introduced, as required. See, e.g., Needleham, et al., (1970) J. Mol. Biol. 48:443-453; Sankoff, et al., (1983) chapter one in Time Warps, String Edits, and Macromolecules: The Theory and Practice of Sequence Comparison, Addison-Wesley, Reading, MA; and software packages from IntelliGenetics, Mountain View, CA; and the University of Wisconsin Genetics Computer Group (GCG), Madison, WI; each of which is incorporated herein by reference. This changes when considering conservative substitutions as matches. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid; asparagine, glutamine; serine, threonine; lysine, arginine; and phenylalanine, tyrosine. Homologous amino acid sequences are intended to include natural allelic and interspecies variations in the cytokine sequence. Typical homologous proteins or peptides will have from 50-100% homology (if gaps can be introduced), to 60-100% homology (if conservative substitutions are included) with an amino acid sequence segment of Table 1. Homology measures will be at least about 70%, generally at least 76%, more generally at least 81%, often at least 85%, more often at least 88%, typically at least 90%, more typically at least 92%, usually at least 94%, more usually at least 95%, preferably at least 96%, and more preferably at least 97%, and in particularly preferred embodiments, at least 98% or more. The degree of homology will vary with the length of the compared segments. Homologous proteins or peptides, such as the allelic variants, will share most biological activities with the embodiments described in Table 1.

As used herein, the term "biological activity" is used to describe, without limitation, effects on inflammatory responses, innate immunity, and/or morphogenic development by cytokine-like ligands. For example, these receptors should mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738. The receptors, or portions thereof, may be useful as phosphate labeling enzymes to label general or specific substrates. The subunits may also be functional immunogens to elicit recognizing antibodies, or antigens capable of binding antibodies.

The terms ligand, agonist, antagonist, and analog of, e.g., a DCRS1, include molecules that modulate the characteristic cellular responses to cytokine ligand proteins, as well as molecules possessing the more standard structural binding competition features of ligand-receptor interactions, e.g., where the receptor is a natural receptor or an antibody. The cellular responses likely are typically mediated through receptor tyrosine kinase pathways.

Also, a ligand is a molecule which serves either as a natural ligand to which said receptor, or an analog thereof, binds, or a molecule which is a functional analog of the natural ligand. The functional analog may be a ligand with structural modifications, or may be a wholly unrelated molecule which has a molecular shape which interacts with the appropriate ligand binding determinants. The ligands may serve as agonists or antagonists, see, e.g., Goodman, et al. (eds. 1990) Goodman & Gilman's: The Pharmacological Bases of Therapeutics, Pergamon Press, New York.

Rational drug design may also be based upon structural studies of the molecular shapes of a receptor or antibody and other effectors or ligands. See, e.g., Herz, et al. (1997) J. Recept. Signal Transduct. Res. 17:671-776; and Chaiken, et al. (1996) Trends Biotechnol. 14:369-375. Effectors may be other proteins which mediate other functions in response to ligand binding, or other proteins which normally interact with the receptor. One means for determining which sites interact with specific other proteins is a physical structure determination, e.g., x-ray crystallography or 2 dimensional NMR techniques. These will provide guidance as to which amino acid residues form molecular contact regions. For a detailed description of protein structural determination, see, e.g., Blundell and Johnson (1976) Protein Crystallography, Academic Press, New York, which is hereby incorporated herein by reference.

## II. Activities

The cytokine receptor-like proteins will have a number of different biological activities, e.g., modulating cell proliferation, or in phosphate metabolism, being added to or removed from specific substrates, typically proteins. Such will generally result in modulation of an inflammatory function, other innate immunity response, or a morphological effect. The subunit will probably have a specific low affinity binding to the ligand.

The DCRS1 has the characteristic motifs of a receptor signaling through the JAK pathway. See, e.g., Ihle, et al. (1997) Stem Cells 15(suppl. 1):105-111; Silvennoinen, et al. (1997) APMIS 105:497-509; Levy (1997) Cytokine Growth Factor Review 8:81-90; Winston and Hunter (1996) Current Biol. 6:668-671; Barrett (1996) Baillieres Clin. Gastroenterol. 10:1-15; and Briscoe, et al. (1996) Philos. Trans. R. Soc. Lond. B. Biol. Sci. 351:167-171.



The biological activities of the cytokine receptor subunits will be related to addition or removal of phosphate moieties to substrates, typically in a specific manner, but occasionally in a non specific manner.

- 5 Substrates may be identified, or conditions for enzymatic activity may be assayed by standard methods, e.g., as described in Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; 10 Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

- The receptor subunits may combine to form functional 15 complexes, e.g., which may be useful for binding ligand or preparing antibodies. These will have substantial diagnostic uses, including detection or quantitation.

### III. Nucleic Acids

- 20 This invention contemplates use of isolated nucleic acid or fragments, e.g., which encode these or closely related proteins, or fragments thereof, e.g., to encode a corresponding polypeptide, preferably one which is biologically active. In addition, this invention covers 25 isolated or recombinant DNAs which encode combinations of such proteins or polypeptides having characteristic sequences, e.g., of the DCRS1s. Typically, the nucleic acid is capable of hybridizing, under appropriate conditions, with a nucleic acid sequence segment shown in 30 Table 1, but preferably not with a corresponding segment of other receptors described in Table 3. Said biologically active protein or polypeptide can be a full length protein, or fragment, and will typically have a segment of amino acid sequence highly homologous, e.g., 35 exhibiting significant stretches of identity, to one shown in Table 1. Further, this invention covers the use of isolated or recombinant nucleic acid, or fragments thereof, which encode proteins having fragments which are

equivalent to the DCRS1 proteins. The isolated nucleic acids can have the respective regulatory sequences in the 5' and 3' flanks, e.g., promoters, enhancers, poly-A addition signals, and others from the natural gene.

5 Combinations, as described, are also provided.

An "isolated" nucleic acid is a nucleic acid, e.g., an RNA, DNA, or a mixed polymer, which is substantially pure, e.g., separated from other components which naturally accompany a native sequence, such as ribosomes, polymerases, and flanking genomic sequences from the originating species. The term embraces a nucleic acid sequence which has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates, which are thereby distinguishable from naturally occurring compositions, and chemically synthesized analogs or analogs biologically synthesized by heterologous systems. A substantially pure molecule includes isolated forms of the molecule, either completely or substantially pure.

20 An isolated nucleic acid will generally be a homogeneous composition of molecules, but will, in some embodiments, contain heterogeneity, preferably minor. This heterogeneity is typically found at the polymer ends or portions not critical to a desired biological function or activity.

25 A "recombinant" nucleic acid is typically defined either by its method of production or its structure. In reference to its method of production, e.g., a product made by a process, the process is use of recombinant nucleic acid techniques, e.g., involving human intervention in the nucleotide sequence. Typically this intervention involves in vitro manipulation, although under certain circumstances it may involve more classical animal breeding techniques. Alternatively, it can be a nucleic acid made by generating a sequence comprising fusion of two fragments which are not naturally contiguous to each other, but is meant to exclude products of nature, e.g., naturally occurring mutants as

found in their natural state. Thus, for example, products made by transforming cells with an unnaturally occurring vector is encompassed, as are nucleic acids comprising sequence derived using any synthetic  
5 oligonucleotide process. Such a process is often done to replace a codon with a redundant codon encoding the same or a conservative amino acid, while typically introducing or removing a restriction enzyme sequence recognition site. Alternatively, the process is performed to join  
10 together nucleic acid segments of desired functions to generate a single genetic entity comprising a desired combination of functions not found in the commonly available natural forms, e.g., encoding a fusion protein. Restriction enzyme recognition sites are often the target  
15 of such artificial manipulations, but other site specific targets, e.g., promoters, DNA replication sites, regulation sequences, control sequences, or other useful features may be incorporated by design. A similar concept is intended for a recombinant, e.g., fusion,  
20 polypeptide. This will include a dimeric repeat. Specifically included are synthetic nucleic acids which, by genetic code redundancy, encode equivalent polypeptides to fragments of DCRS1 and fusions of sequences from various different related molecules, e.g.,  
25 other cytokine receptor family members.

A "fragment" in a nucleic acid context is a contiguous segment of at least about 17 nucleotides, generally at least 21 nucleotides, more generally at least 25 nucleotides, ordinarily at least 30 nucleotides,  
30 more ordinarily at least 35 nucleotides, often at least 39 nucleotides, more often at least 45 nucleotides, typically at least 50 nucleotides, more typically at least 55 nucleotides, usually at least 60 nucleotides, more usually at least 66 nucleotides, preferably at least  
35 72 nucleotides, more preferably at least 79 nucleotides, and in particularly preferred embodiments will be at least 85 or more nucleotides. Typically, fragments of different genetic sequences can be compared to one

another over appropriate length stretches, particularly defined segments such as the domains described below.

A nucleic acid which codes for the DCRS1 will be particularly useful to identify genes, mRNA, and cDNA species which code for itself or closely related proteins, as well as DNAs which code for polymorphic, allelic, or other genetic variants, e.g., from different individuals or related species. Preferred probes for such screens are those regions of the interleukin which are conserved between different polymorphic variants or which contain nucleotides which lack specificity, and will preferably be full length or nearly so. In other situations, polymorphic variant specific sequences will be more useful.

Nucleic acids encoding various combinations including, e.g., the DSRS1, the DCRS1, and/or the IL-B30, will be useful for coexpression of the proteins together. Such will be useful, e.g., in producing complexes, for production of antibodies or screening for ligands.

This invention further covers recombinant nucleic acid molecules and fragments having a nucleic acid sequence identical to or highly homologous to the isolated DNA set forth herein. In particular, the sequences will often be operably linked to DNA segments which control transcription, translation, and DNA replication. These additional segments typically assist in expression of the desired nucleic acid segment.

Homologous, or highly identical, nucleic acid sequences, when compared to one another, e.g., DCRS1 sequences, exhibit significant similarity. The standards for homology in nucleic acids are either measures for homology generally used in the art by sequence comparison or based upon hybridization conditions. Comparative hybridization conditions are described in greater detail below.

Substantial identity in the nucleic acid sequence comparison context means either that the segments, or their complementary strands, when compared, are identical

when optimally aligned, with appropriate nucleotide insertions or deletions, in at least about 60% of the nucleotides, generally at least 66%, ordinarily at least 71%, often at least 76%, more often at least 80%, usually at least 84%, more usually at least 88%, typically at least 91%, more typically at least about 93%, preferably at least about 95%, more preferably at least about 96 to 98% or more, and in particular embodiments, as high at about 99% or more of the nucleotides, including, e.g., segments encoding structural domains such as the segments described below. Alternatively, substantial identity will exist when the segments will hybridize under selective hybridization conditions, to a strand or its complement, typically using a sequence derived from Table 1. Typically, selective hybridization will occur when there is at least about 55% homology over a stretch of at least about 14 nucleotides, more typically at least about 65%, preferably at least about 75%, and more preferably at least about 90%. See, Kanehisa (1984) Nucl. Acids Res. 12:203-213, which is incorporated herein by reference. The length of homology comparison, as described, may be over longer stretches, and in certain embodiments will be over a stretch of at least about 17 nucleotides, generally at least about 20 nucleotides, ordinarily at least about 24 nucleotides, usually at least about 28 nucleotides, typically at least about 32 nucleotides, more typically at least about 40 nucleotides, preferably at least about 50 nucleotides, and more preferably at least about 75 to 100 or more nucleotides. This includes, e.g., 125, 150, 175, 200, 225, 246, 273, and other lengths.

Stringent conditions, in referring to homology in the hybridization context, will be stringent combined conditions of salt, temperature, organic solvents, and other parameters typically controlled in hybridization reactions. Stringent temperature conditions will usually include temperatures in excess of about 30° C, more usually in excess of about 37° C, typically in excess of

about 45° C, more typically in excess of about 55° C, preferably in excess of about 65° C, and more preferably in excess of about 70° C. Stringent salt conditions will ordinarily be less than about 500 mM, usually less than  
5 about 400 mM, more usually less than about 300 mM, typically less than about 200 mM, preferably less than about 100 mM, and more preferably less than about 80 mM, even down to less than about 20 mM. However, the combination of parameters is much more important than the  
10 measure of any single parameter. See, e.g., Wetmur and Davidson (1968) J. Mol. Biol. 31:349-370, which is hereby incorporated herein by reference.

The isolated DNA can be readily modified by nucleotide substitutions, nucleotide deletions,  
15 nucleotide insertions, and inversions of nucleotide stretches. These modifications result in novel DNA sequences which encode this protein or its derivatives. These modified sequences can be used to produce mutant proteins (muteins) or to enhance the expression of  
20 variant species. Enhanced expression may involve gene amplification, increased transcription, increased translation, and other mechanisms. Such mutant DCRS1-like derivatives include predetermined or site-specific mutations of the protein or its fragments, including  
25 silent mutations using genetic code degeneracy. "Mutant DCRS1" as used herein encompasses a polypeptide otherwise falling within the homology definition of the DCRS1 as set forth above, but having an amino acid sequence which differs from that of other cytokine receptor-like  
30 proteins as found in nature, whether by way of deletion, substitution, or insertion. In particular, "site specific mutant DCRS1" encompasses a protein having substantial sequence identity with a protein of Table 1, and typically shares most of the biological activities or  
35 effects of the forms disclosed herein.

Although site specific mutation sites are predetermined, mutants need not be site specific. Mammalian DCRS1 mutagenesis can be achieved by making

amino acid insertions or deletions in the gene, coupled with expression. Substitutions, deletions, insertions, or many combinations may be generated to arrive at a final construct. Insertions include amino- or carboxy-terminal fusions. Random mutagenesis can be conducted at a target codon and the expressed mammalian DCRS1 mutants can then be screened for the desired activity, providing some aspect of a structure-activity relationship.

Methods for making substitution mutations at predetermined sites in DNA having a known sequence are well known in the art, e.g., by M13 primer mutagenesis. See also Sambrook, et al. (1989) and Ausubel, et al. (1987 and periodic Supplements).

The mutations in the DNA normally should not place coding sequences out of reading frames and preferably will not create complementary regions that could hybridize to produce secondary mRNA structure such as loops or hairpins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Polymerase chain reaction (PCR) techniques can often be applied in mutagenesis. Alternatively, mutagenesis primers are commonly used methods for generating defined mutations at predetermined sites. See, e.g., Innis, et al. (eds. 1990) PCR Protocols: A Guide to Methods and Applications Academic Press, San Diego, CA; and Dieffenbach and Dveksler (1995; eds.) PCR Primer: A Laboratory Manual Cold Spring Harbor Press, CSH, NY.

Certain embodiments of the invention are directed to combination compositions comprising the receptor or ligand sequences described. In other embodiments, functional portions of the sequences may be joined to

encode fusion proteins. In other forms, variants of the described sequences may be substituted in the combinations.

5 IV. Proteins, Peptides

As described above, the present invention encompasses primate DCRS1, e.g., whose sequences are disclosed in Table 1, and described above. Allelic and other variants are also contemplated, including, e.g.,  
10 fusion proteins combining portions of such sequences with others, including, e.g., epitope tags and functional domains.

The present invention also provides recombinant proteins, e.g., heterologous fusion proteins using  
15 segments from these primate or rodent proteins. A heterologous fusion protein is a fusion of proteins or segments which are naturally not normally fused in the same manner. Thus, the fusion product of a DCRS1 with another cytokine receptor is a continuous protein  
20 molecule having sequences fused in a typical peptide linkage, typically made as a single translation product and exhibiting properties, e.g., sequence or antigenicity, derived from each source peptide. A similar concept applies to heterologous nucleic acid  
25 sequences. Combinations of various designated proteins into complexes are also provided.

In addition, new constructs may be made from combining similar functional or structural domains from other related proteins, e.g., cytokine receptors or Toll-  
30 like receptors, including species variants. For example, ligand-binding or other segments may be "swapped" between different new fusion polypeptides or fragments. See, e.g., Cunningham, et al. (1989) Science 243:1330-1336; and O'Dowd, et al. (1988) J. Biol. Chem. 263:15985-15992,  
35 each of which is incorporated herein by reference. Thus, new chimeric polypeptides exhibiting new combinations of specificities will result from the functional linkage of receptor-binding specificities. For example, the ligand



binding domains from other related receptor molecules may be added or substituted for other domains of this or related proteins. The resulting protein will often have hybrid function and properties. For example, a fusion  
5 protein may include a targeting domain which may serve to provide sequestering of the fusion protein to a particular subcellular organelle.

Candidate fusion partners and sequences can be selected from various sequence data bases, e.g., GenBank,  
10 c/o IntelliGenetics, Mountain View, CA; and BCG, University of Wisconsin Biotechnology Computing Group, Madison, WI, which are each incorporated herein by reference. In particular, combinations of polypeptide sequences provided in Tables 1, 4, or 6 are particularly  
15 preferred. Variant forms of the proteins may be substituted in the described combinations. In certain embodiments, portions of the DSRS1 may be fused to portions of the IL-B30.

The present invention particularly provides muteins  
20 which bind cytokine-like ligands, and/or which are affected in signal transduction. Structural alignment of human DCRS1 with other members of the cytokine receptor family show conserved features/residues. See Table 3. Alignment of the human DCRS1 sequence with other members  
25 of the cytokine receptor family indicates various structural and functionally shared features. See also, Bazan, et al. (1996) Nature 379:591; Lodi, et al. (1994) Science 263:1762-1766; Sayle and Milner-White (1995) TIBS 20:374-376; and Gronenberg, et al. (1991) Protein  
30 Engineering 4:263-269.

Substitutions with either mouse sequences or human sequences are particularly preferred. Conversely, conservative substitutions away from the ligand binding interaction regions will probably preserve most signaling  
35 activities; and conservative substitutions away from the intracellular domains will probably preserve most ligand binding properties.

"Derivatives" of the primate DCRS1 include amino acid sequence mutants, glycosylation variants, metabolic derivatives and covalent or aggregative conjugates with other chemical moieties. Covalent derivatives can be prepared by linkage of functionalities to groups which are found in the DCRS1 amino acid side chains or at the N- or C- termini, e.g., by means which are well known in the art. These derivatives can include, without limitation, aliphatic esters or amides of the carboxyl terminus, or of residues containing carboxyl side chains, O-acyl derivatives of hydroxyl group-containing residues, and N-acyl derivatives of the amino terminal amino acid or amino-group containing residues, e.g., lysine or arginine. Acyl groups are selected from the group of alkyl-moieties, including C3 to C18 normal alkyl, thereby forming alkanoyl aroyl species.

In particular, glycosylation alterations are included, e.g., made by modifying the glycosylation patterns of a polypeptide during its synthesis and processing, or in further processing steps. Particularly preferred means for accomplishing this are by exposing the polypeptide to glycosylating enzymes derived from cells which normally provide such processing, e.g., mammalian glycosylation enzymes. Deglycosylation enzymes are also contemplated. Also embraced are versions of the same primary amino acid sequence which have other minor modifications, including phosphorylated amino acid residues, e.g., phosphotyrosine, phosphoserine, or phosphothreonine.

A major group of derivatives are covalent conjugates of the receptors or fragments thereof with other proteins of polypeptides. These derivatives can be synthesized in recombinant culture such as N- or C-terminal fusions or by the use of agents known in the art for their usefulness in cross-linking proteins through reactive side groups. Preferred derivatization sites with cross-linking agents are at free amino groups, carbohydrate moieties, and cysteine residues.

Fusion polypeptides between the receptors and other homologous or heterologous proteins are also provided. Homologous polypeptides may be fusions between different receptors, resulting in, for instance, a hybrid protein exhibiting binding specificity for multiple different cytokine ligands, or a receptor which may have broadened or weakened specificity of substrate effect. Likewise, heterologous fusions may be constructed which would exhibit a combination of properties or activities of the derivative proteins. Typical examples are fusions of a reporter polypeptide, e.g., luciferase, with a segment or domain of a receptor, e.g., a ligand-binding segment, so that the presence or location of a desired ligand may be easily determined. See, e.g., Dull, et al., U.S. Patent No. 4,859,609, which is hereby incorporated herein by reference. Other gene fusion partners include glutathione-S-transferase (GST), bacterial  $\beta$ -galactosidase, trpE, Protein A,  $\beta$ -lactamase, alpha amylase, alcohol dehydrogenase, and yeast alpha mating factor. See, e.g., Godowski, et al. (1988) Science 241:812-816. Labeled proteins will often be substituted in the described combinations of proteins.

The phosphoramidite method described by Beaucage and Carruthers (1981) Tetra. Letts. 22:1859-1862, will produce suitable synthetic DNA fragments. A double stranded fragment will often be obtained either by synthesizing the complementary strand and annealing the strand together under appropriate conditions or by adding the complementary strand using DNA polymerase with an appropriate primer sequence.

Such polypeptides may also have amino acid residues which have been chemically modified by phosphorylation, sulfonation, biotinylation, or the addition or removal of other moieties, particularly those which have molecular shapes similar to phosphate groups. In some embodiments, the modifications will be useful labeling reagents, or serve as purification targets, e.g., affinity ligands.

Fusion proteins will typically be made by either recombinant nucleic acid methods or by synthetic polypeptide methods. Techniques for nucleic acid manipulation and expression are described generally, for example, in Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual (2d ed.), Vols. 1-3, Cold Spring Harbor Laboratory, and Ausubel, et al. (eds. 1987 and periodic supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York, which are each incorporated herein by reference. Techniques for synthesis of polypeptides are described, for example, in Merrifield (1963) J. Amer. Chem. Soc. 85:2149-2156; Merrifield (1986) Science 232: 341-347; and Atherton, et al. (1989) Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford; each of which is incorporated herein by reference. See also Dawson, et al. (1994) Science 266:776-779 for methods to make larger polypeptides.

This invention also contemplates the use of derivatives of a DCRS1 other than variations in amino acid sequence or glycosylation. Such derivatives may involve covalent or aggregative association with chemical moieties. These derivatives generally fall into three classes: (1) salts, (2) side chain and terminal residue covalent modifications, and (3) adsorption complexes, for example with cell membranes. Such covalent or aggregative derivatives are useful as immunogens, as reagents in immunoassays, or in purification methods such as for affinity purification of a receptor or other binding molecule, e.g., an antibody. For example, a cytokine ligand can be immobilized by covalent bonding to a solid support such as cyanogen bromide-activated Sepharose, by methods which are well known in the art, or adsorbed onto polyolefin surfaces, with or without glutaraldehyde cross-linking, for use in the assay or purification of a cytokine receptor, antibodies, or other similar molecules. The ligand can also be labeled with a detectable group, for example radioiodinated by the chloramine T procedure, covalently bound to rare earth

chelates, or conjugated to another fluorescent moiety for use in diagnostic assays.

A combination, e.g., including a DCRS1, of this invention can be used as an immunogen for the production  
5 of antisera or antibodies specific, e.g., capable of distinguishing between other cytokine receptor family members, for the combinations described. The complexes can be used to screen monoclonal antibodies or antigen-binding fragments prepared by immunization with various  
10 forms of impure preparations containing the protein. In particular, the term "antibodies" also encompasses antigen binding fragments of natural antibodies, e.g., Fab, Fab2, Fv, etc. The purified DCRS1 can also be used as a reagent to detect antibodies generated in response  
15 to the presence of elevated levels of expression, or immunological disorders which lead to antibody production to the endogenous receptor. Additionally, DCRS1 fragments may also serve as immunogens to produce the antibodies of the present invention, as described  
20 immediately below. For example, this invention contemplates antibodies having binding affinity to or being raised against the amino acid sequences shown in Table 1, fragments thereof, or various homologous peptides. In particular, this invention contemplates  
25 antibodies having binding affinity to, or having been raised against, specific fragments which are predicted to be, or actually are, exposed at the exterior protein surface of the native DCRS1. Complexes of combinations of proteins will also be useful, and antibody  
30 preparations thereto can be made.

The blocking of physiological response to the receptor ligands may result from the inhibition of binding of the ligand to the receptor, likely through competitive inhibition. Thus, in vitro assays of the  
35 present invention will often use antibodies or antigen binding segments of these antibodies, or fragments attached to solid phase substrates. These assays will also allow for the diagnostic determination of the

effects of either ligand binding region mutations and modifications, or other mutations and modifications, e.g., which affect signaling or enzymatic function.

This invention also contemplates the use of  
5 competitive drug screening assays, e.g., where neutralizing antibodies to the receptor complexes or fragments compete with a test compound for binding to a ligand or other antibody. In this manner, the neutralizing antibodies or fragments can be used to  
10 detect the presence of a polypeptide which shares one or more binding sites to a receptor and can also be used to occupy binding sites on a receptor that might otherwise bind a ligand.

15 V. Making Nucleic Acids and Protein

DNA which encodes the protein or fragments thereof can be obtained by chemical synthesis, screening cDNA libraries, or by screening genomic libraries prepared from a wide variety of cell lines or tissue samples.  
20 Natural sequences can be isolated using standard methods and the sequences provided herein, e.g., in Table 1. Other species counterparts can be identified by hybridization techniques, or by various PCR techniques, combined with or by searching in sequence databases,  
25 e.g., GenBank.

This DNA can be expressed in a wide variety of host cells for the synthesis of a full-length receptor or fragments which can in turn, for example, be used to generate polyclonal or monoclonal antibodies; for binding  
30 studies; for construction and expression of modified ligand binding or kinase/phosphatase domains; and for structure/function studies. Variants or fragments can be expressed in host cells that are transformed or transfected with appropriate expression vectors. These  
35 molecules can be substantially free of protein or cellular contaminants, other than those derived from the recombinant host; and therefore are particularly useful in pharmaceutical compositions when combined with a

pharmaceutically acceptable carrier and/or diluent. The protein, or portions thereof, may be expressed as fusions with other proteins. Combinations of the described proteins, or nucleic acids encoding them, are particularly interesting.

Expression vectors are typically self-replicating DNA or RNA constructs containing the desired receptor gene or its fragments, usually operably linked to suitable genetic control elements that are recognized in a suitable host cell. These control elements are capable of effecting expression within a suitable host. The multiple genes may be coordinately expressed, and may be on a polycistronic message. The specific type of control elements necessary to effect expression will depend upon the eventual host cell used. Generally, the genetic control elements can include a prokaryotic promoter system or a eukaryotic promoter expression control system, and typically include a transcriptional promoter, an optional operator to control the onset of transcription, transcription enhancers to elevate the level of mRNA expression, a sequence that encodes a suitable ribosome binding site, and sequences that terminate transcription and translation. Expression vectors also usually contain an origin of replication that allows the vector to replicate independently of the host cell.

The vectors of this invention include those which contain DNA which encodes a combination of proteins, as described, or a biologically active equivalent polypeptide. The DNA can be under the control of a viral promoter and can encode a selection marker. This invention further contemplates use of such expression vectors which are capable of expressing eukaryotic cDNAs coding for such proteins in a prokaryotic or eukaryotic host, where the vector is compatible with the host and where the eukaryotic cDNAs are inserted into the vector such that growth of the host containing the vector expresses the cDNAs in question. Usually, expression

vectors are designed for stable replication in their host cells or for amplification to greatly increase the total number of copies of the desirable gene per cell. It is not always necessary to require that an expression vector  
5 replicate in a host cell, e.g., it is possible to effect transient expression of the protein or its fragments in various hosts using vectors that do not contain a replication origin that is recognized by the host cell. It is also possible to use vectors that cause integration  
10 of the protein encoding portions into the host DNA by recombination.

Vectors, as used herein, comprise plasmids, viruses, bacteriophage, integratable DNA fragments, and other vehicles which enable the integration of DNA fragments  
15 into the genome of the host. Expression vectors are specialized vectors which contain genetic control elements that effect expression of operably linked genes. Plasmids are the most commonly used form of vector but all other forms of vectors which serve an equivalent  
20 function and which are, or become, known in the art are suitable for use herein. See, e.g., Pouwels, et al. (1985 and Supplements) Cloning Vectors: A Laboratory Manual, Elsevier, N.Y., and Rodriguez, et al. (eds. 1988) Vectors: A Survey of Molecular Cloning Vectors and Their  
25 Uses, Butterworth, Boston, which are incorporated herein by reference.

Transformed cells are cells, preferably mammalian, that have been transformed or transfected with vectors constructed using recombinant DNA techniques.  
30 Transformed host cells usually express the desired proteins, but for purposes of cloning, amplifying, and manipulating its DNA, do not need to express the subject proteins. This invention further contemplates culturing transformed cells in a nutrient medium, thus permitting  
35 the proteins to accumulate. The proteins can be recovered, either from the culture or, in certain instances, from the culture medium.



For purposes of this invention, nucleic sequences are operably linked when they are functionally related to each other. For example, DNA for a presequence or secretory leader is operably linked to a polypeptide if it is expressed as a preprotein or participates in directing the polypeptide to the cell membrane or in secretion of the polypeptide. A promoter is operably linked to a coding sequence if it controls the transcription of the polypeptide; a ribosome binding site is operably linked to a coding sequence if it is positioned to permit translation. Usually, operably linked means contiguous and in reading frame, however, certain genetic elements such as repressor genes are not contiguously linked but still bind to operator sequences that in turn control expression.

Suitable host cells include prokaryotes, lower eukaryotes, and higher eukaryotes. Prokaryotes include both gram negative and gram positive organisms, e.g., E. coli and B. subtilis. Lower eukaryotes include yeasts, e.g., S. cerevisiae and Pichia, and species of the genus Dictyostelium. Higher eukaryotes include established tissue culture cell lines from animal cells, both of non-mammalian origin, e.g., insect cells, and birds, and of mammalian origin, e.g., human, primates, and rodents.

Prokaryotic host-vector systems include a wide variety of vectors for many different species. As used herein, E. coli and its vectors will be used generically to include equivalent vectors used in other prokaryotes. A representative vector for amplifying DNA is pBR322 or many of its derivatives. Vectors that can be used to express the receptor or its fragments include, but are not limited to, such vectors as those containing the lac promoter (pUC-series); trp promoter (pBR322-trp); Ipp promoter (the pIN-series); lambda-pP or pR promoters (pOTS); or hybrid promoters such as ptac (pDR540). See Brosius, et al. (1988) "Expression Vectors Employing Lambda-, trp-, lac-, and Ipp-derived Promoters", in Vectors: A Survey of Molecular Cloning Vectors and Their

Uses, (eds. Rodriguez and Denhardt), Butterworth, Boston, Chapter 10, pp. 205-236, which is incorporated herein by reference.

Lower eukaryotes, e.g., yeasts and Dictyostelium,  
5 may be transformed with DCRS1 sequence containing  
vectors. For purposes of this invention, the most common  
lower eukaryotic host is the baker's yeast, Saccharomyces  
cerevisiae. It will be used to generically represent  
10 lower eukaryotes although a number of other strains and  
species are also available. Yeast vectors typically  
consist of a replication origin (unless of the  
integrating type), a selection gene, a promoter, DNA  
encoding the receptor or its fragments, and sequences for  
translation termination, polyadenylation, and  
15 transcription termination. Suitable expression vectors  
for yeast include such constitutive promoters as  
3-phosphoglycerate kinase and various other glycolytic  
enzyme gene promoters or such inducible promoters as the  
alcohol dehydrogenase 2 promoter or metallothionine  
20 promoter. Suitable vectors include derivatives of the  
following types: self-replicating low copy number (such  
as the YRp-series), self-replicating high copy number  
(such as the YE<sub>p</sub>-series); integrating types (such as the  
YIp-series), or mini-chromosomes (such as the  
25 YC<sub>p</sub>-series).

Higher eukaryotic tissue culture cells are normally  
the preferred host cells for expression of the  
functionally active interleukin or receptor proteins. In  
principle, many higher eukaryotic tissue culture cell  
30 lines are workable, e.g., insect baculovirus expression  
systems, whether from an invertebrate or vertebrate  
source. However, mammalian cells are preferred.  
Transformation or transfection and propagation of such  
cells has become a routine procedure. Examples of useful  
35 cell lines include HeLa cells, Chinese hamster ovary  
(CHO) cell lines, baby rat kidney (BRK) cell lines,  
insect cell lines, bird cell lines, and monkey (COS) cell  
lines. Expression vectors for such cell lines usually

include an origin of replication, a promoter, a translation initiation site, RNA splice sites (if genomic DNA is used), a polyadenylation site, and a transcription termination site. These vectors also usually contain a selection gene or amplification gene. Suitable expression vectors may be plasmids, viruses, or retroviruses carrying promoters derived, e.g., from such sources as from adenovirus, SV40, parvoviruses, vaccinia virus, or cytomegalovirus. Representative examples of suitable expression vectors include pCDNA1; pCD, see Okayama, et al. (1985) Mol. Cell Biol. 5:1136-1142; pMC1neo PolyA, see Thomas, et al. (1987) Cell 51:503-512; and a baculovirus vector such as pAC 373 or pAC 610.

For secreted proteins and some membrane proteins, an open reading frame usually encodes a polypeptide that consists of a mature or secreted product covalently linked at its N-terminus to a signal peptide. The signal peptide is cleaved prior to secretion of the mature, or active, polypeptide. The cleavage site can be predicted with a high degree of accuracy from empirical rules, e.g., von-Heijne (1986) Nucleic Acids Research 14:4683-4690 and Nielsen, et al. (1997) Protein Eng. 10:1-12, and the precise amino acid composition of the signal peptide often does not appear to be critical to its function, e.g., Randall, et al. (1989) Science 243:1156-1159; Kaiser et al. (1987) Science 235:312-317. The mature proteins of the invention can be readily determined using standard methods.

It will often be desired to express these polypeptides in a system which provides a specific or defined glycosylation pattern. In this case, the usual pattern will be that provided naturally by the expression system. However, the pattern will be modifiable by exposing the polypeptide, e.g., an unglycosylated form, to appropriate glycosylating proteins introduced into a heterologous expression system. For example, the receptor gene may be co-transformed with one or more genes encoding mammalian or other glycosylating enzymes.

Using this approach, certain mammalian glycosylation patterns will be achievable in prokaryote or other cells. Expression in prokaryote cells will typically lead to unglycosylated forms of protein.

5       The source of DCRS1 can be a eukaryotic or prokaryotic host expressing recombinant DCRS1, such as is described above. The source can also be a cell line such as mouse Swiss 3T3 fibroblasts, but other mammalian cell lines are also contemplated by this invention, with the  
10       preferred cell line being from the human species.

      Now that the sequences are known, the primate DCRS1, fragments, or derivatives thereof can be prepared by conventional processes for synthesizing peptides. These include processes such as are described in Stewart and  
15       Young (1984) Solid Phase Peptide Synthesis, Pierce Chemical Co., Rockford, IL; Bodanszky and Bodanszky (1984) The Practice of Peptide Synthesis, Springer-Verlag, New York; and Bodanszky (1984) The Principles of Peptide Synthesis, Springer-Verlag, New  
20       York; all of each which are incorporated herein by reference. For example, an azide process, an acid chloride process, an acid anhydride process, a mixed anhydride process, an active ester process (for example, p-nitrophenyl ester, N-hydroxysuccinimide ester, or  
25       cyanomethyl ester), a carbodiimidazole process, an oxidative-reductive process, or a dicyclohexylcarbodiimide (DCCD)/additive process can be used. Solid phase and solution phase syntheses are both applicable to the foregoing processes. Similar  
30       techniques can be used with partial DCRS1 sequences.

      The DCRS1 proteins, fragments, or derivatives are suitably prepared in accordance with the above processes as typically employed in peptide synthesis, generally either by a so-called stepwise process which comprises  
35       condensing an amino acid to the terminal amino acid, one by one in sequence, or by coupling peptide fragments to the terminal amino acid. Amino groups that are not being

used in the coupling reaction typically must be protected to prevent coupling at an incorrect location.

If a solid phase synthesis is adopted, the C-terminal amino acid is bound to an insoluble carrier or support through its carboxyl group. The insoluble carrier is not particularly limited as long as it has a binding capability to a reactive carboxyl group. Examples of such insoluble carriers include halomethyl resins, such as chloromethyl resin or bromomethyl resin, hydroxymethyl resins, phenol resins, tert-alkyloxycarbonylhydrazidated resins, and the like.

An amino group-protected amino acid is bound in sequence through condensation of its activated carboxyl group and the reactive amino group of the previously formed peptide or chain, to synthesize the peptide step by step. After synthesizing the complete sequence, the peptide is split off from the insoluble carrier to produce the peptide. This solid-phase approach is generally described by Merrifield, et al. (1963) in J. Am. Chem. Soc. 85:2149-2156, which is incorporated herein by reference.

The prepared protein and fragments thereof can be isolated and purified from the reaction mixture by means of peptide separation, for example, by extraction, precipitation, electrophoresis, various forms of chromatography, and the like. The receptors of this invention can be obtained in varying degrees of purity depending upon desired uses. Purification can be accomplished by use of the protein purification techniques disclosed herein, see below, or by the use of the antibodies herein described in methods of immunoabsorbant affinity chromatography. This immunoabsorbant affinity chromatography is carried out by first linking the antibodies to a solid support and then contacting the linked antibodies with solubilized lysates of appropriate cells, lysates of other cells expressing the receptor, or lysates or supernatants of cells

producing the protein as a result of DNA techniques, see below.

Generally, the purified protein will be at least about 40% pure, ordinarily at least about 50% pure, usually at least about 60% pure, typically at least about 70% pure, more typically at least about 80% pure, preferable at least about 90% pure and more preferably at least about 95% pure, and in particular embodiments, 97%-99% or more. Purity will usually be on a weight basis, but can also be on a molar basis. Different assays will be applied as appropriate. Individual proteins may be purified and thereafter combined.

#### VI. Antibodies

Antibodies can be raised to the various mammalian, e.g., primate DCRS1 proteins and fragments thereof, both in naturally occurring native forms and in their recombinant forms, the difference being that antibodies to the active receptor are more likely to recognize epitopes which are only present in the native conformations. Denatured antigen detection can also be useful in, e.g., Western analysis. Anti-idiotypic antibodies are also contemplated, which would be useful as agonists or antagonists of a natural receptor or an antibody.

Antibodies, including binding fragments and single chain versions, against predetermined fragments of the protein can be raised by immunization of animals with conjugates of the fragments with immunogenic proteins. Monoclonal antibodies are prepared from cells secreting the desired antibody. These antibodies can be screened for binding to normal or defective protein, or screened for agonistic or antagonistic activity. These monoclonal antibodies will usually bind with at least a  $K_D$  of about 1 mM, more usually at least about 300  $\mu$ M, typically at least about 100 $\mu$ M, more typically at least about 30  $\mu$ M, preferably at least about 10  $\mu$ M, and more preferably at least about 3  $\mu$ M or better.

The antibodies, including antigen binding fragments, of this invention can have significant diagnostic or therapeutic value. They can be potent antagonists that bind to the receptor and inhibit binding to ligand or inhibit the ability of the receptor to elicit a biological response, e.g., act on its substrate. They also can be useful as non-neutralizing antibodies and can be coupled to toxins or radionuclides to bind producing cells, or cells localized to the source of the interleukin. Further, these antibodies can be conjugated to drugs or other therapeutic agents, either directly or indirectly by means of a linker.

The antibodies of this invention can also be useful in diagnostic applications. As capture or non-neutralizing antibodies, they might bind to the receptor without inhibiting ligand or substrate binding. As neutralizing antibodies, they can be useful in competitive binding assays. They will also be useful in detecting or quantifying ligand. They may be used as reagents for Western blot analysis, or for immunoprecipitation or immunopurification of the respective protein. Likewise, nucleic acids and proteins may be immobilized to solid substrates for affinity purification or detection methods. The substrates may be, e.g., solid resin beads or sheets of plastic.

Protein fragments may be joined to other materials, particularly polypeptides, as fused or covalently joined polypeptides to be used as immunogens. Mammalian cytokine receptors and fragments may be fused or covalently linked to a variety of immunogens, such as keyhole limpet hemocyanin, bovine serum albumin, tetanus toxoid, etc. See Microbiology, Hoeber Medical Division, Harper and Row, 1969; Landsteiner (1962) Specificity of Serological Reactions, Dover Publications, New York; and Williams, et al. (1967) Methods in Immunology and Immunochemistry, Vol. 1, Academic Press, New York; each of which are incorporated herein by reference, for descriptions of methods of preparing polyclonal antisera.

A typical method involves hyperimmunization of an animal with an antigen. The blood of the animal is then collected shortly after the repeated immunizations and the gamma globulin is isolated.

5 In some instances, it is desirable to prepare monoclonal antibodies from various mammalian hosts, such as mice, rodents, primates, humans, etc. Description of techniques for preparing such monoclonal antibodies may be found in, e.g., Stites, et al. (eds.) Basic and  
10 Clinical Immunology (4th ed.), Lange Medical Publications, Los Altos, CA, and references cited therein; Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH Press; Goding (1986) Monoclonal Antibodies: Principles and Practice (2d ed) Academic Press, New York;  
15 and particularly in Kohler and Milstein (1975) in Nature 256: 495-497, which discusses one method of generating monoclonal antibodies. Each of these references is incorporated herein by reference. Summarized briefly, this method involves injecting an animal with an  
20 immunogen. The animal is then sacrificed and cells taken from its spleen, which are then fused with myeloma cells. The result is a hybrid cell or "hybridoma" that is capable of reproducing in vitro. The population of hybridomas is then screened to isolate individual clones,  
25 each of which secrete a single antibody species to the immunogen. In this manner, the individual antibody species obtained are the products of immortalized and cloned single B cells from the immune animal generated in response to a specific site recognized on the immunogenic  
30 substance.

Other suitable techniques involve in vitro exposure of lymphocytes to the antigenic polypeptides or alternatively to selection of libraries of antibodies in phage or similar vectors. See, Huse, et al. (1989)  
35 "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science 246:1275-1281; and Ward, et al. (1989) Nature 341:544-546, each of which is hereby incorporated herein by



reference. The polypeptides and antibodies of the present invention may be used with or without modification, including chimeric or humanized antibodies. Frequently, the polypeptides and antibodies will be  
5 labeled by joining, either covalently or non-covalently, a substance which provides for a detectable signal. A wide variety of labels and conjugation techniques are known and are reported extensively in both the scientific and patent literature. Suitable labels include  
10 radionuclides, enzymes, substrates, cofactors, inhibitors, fluorescent moieties, chemiluminescent moieties, magnetic particles, and the like. Patents, teaching the use of such labels include U.S. Patent Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437;  
15 4,275,149; and 4,366,241. Also, recombinant or chimeric immunoglobulins may be produced, see Cabilly, U.S. Patent No. 4,816,567; or made in transgenic mice, see Mendez, et al. (1997) Nature Genetics 15:146-156. These references are incorporated herein by reference.

20 The antibodies of this invention can also be used for affinity chromatography in isolating the DCRS1 proteins or peptides. Columns can be prepared where the antibodies are linked to a solid support, e.g., particles, such as agarose, Sephadex, or the like, where  
25 a cell lysate may be passed through the column, the column washed, followed by increasing concentrations of a mild denaturant, whereby the purified protein will be released. Alternatively, the protein may be used to purify antibody. Appropriate cross absorptions or  
30 depletions may be applied.

The antibodies may also be used to screen expression libraries for particular expression products. Usually the antibodies used in such a procedure will be labeled with a moiety allowing easy detection of presence of  
35 antigen by antibody binding.

Antibodies raised against a cytokine receptor will also be used to raise anti-idiotypic antibodies. These will be useful in detecting or diagnosing various

immunological conditions related to expression of the protein or cells which express the protein. They also will be useful as agonists or antagonists of the ligand, which may be competitive inhibitors or substitutes for naturally occurring ligands.

A cytokine receptor protein that specifically binds to or that is specifically immunoreactive with an antibody generated against a defined immunogen, such as an immunogen consisting of the amino acid sequence of SEQ ID NO: 13, is typically determined in an immunoassay. The immunoassay typically uses a polyclonal antiserum which was raised, e.g., to a protein of SEQ ID NO: 13. This antiserum is selected to have low crossreactivity against other cytokine receptor family members, e.g., IL-12 receptor beta or gp130, preferably from the same species, and any such crossreactivity is removed by immunoabsorption prior to use in the immunoassay.

In order to produce antisera for use in an immunoassay, the protein, e.g., of SEQ ID NO: 13, is isolated as described herein. For example, recombinant protein may be produced in a mammalian cell line. An appropriate host, e.g., an inbred strain of mice such as Balb/c, is immunized with the selected protein, typically using a standard adjuvant, such as Freund's adjuvant, and a standard mouse immunization protocol (see Harlow and Lane, supra). Alternatively, a synthetic peptide derived from the sequences disclosed herein and conjugated to a carrier protein can be used as an immunogen. Polyclonal sera are collected and titrated against the immunogen protein in an immunoassay, e.g., a solid phase immunoassay with the immunogen immobilized on a solid support. Polyclonal antisera with a titer of  $10^4$  or greater are selected and tested for their cross reactivity against other cytokine receptor family members, e.g., IL-12 receptor beta and/or gp130, using a competitive binding immunoassay such as the one described in Harlow and Lane, supra, at pages 570-573. Preferably at least two cytokine receptor family members are used in

this determination. These cytokine receptor family members can be produced as recombinant proteins and isolated using standard molecular biology and protein chemistry techniques as described herein.

- 5       Immunoassays in the competitive binding format can be used for the crossreactivity determinations. For example, the protein of SEQ ID NO: 13 can be immobilized to a solid support. Proteins added to the assay compete with the binding of the antisera to the immobilized
- 10   antigen. The ability of the above proteins to compete with the binding of the antisera to the immobilized protein is compared to the proteins of IL-12 receptor beta or gp130. The percent crossreactivity for the above proteins is calculated, using standard calculations.
- 15   Those antisera with less than 10% crossreactivity with each of the proteins listed above are selected and pooled. The cross-reacting antibodies are then removed from the pooled antisera by immunoabsorption with the above-listed proteins.
- 20       The immunoabsorbed and pooled antisera are then used in a competitive binding immunoassay as described above to compare a second protein to the immunogen protein (e.g., the DCRS1 like protein of SEQ ID NO: 13). In order to make this comparison, the two proteins are each
- 25   assayed at a wide range of concentrations and the amount of each protein required to inhibit 50% of the binding of the antisera to the immobilized protein is determined. If the amount of the second protein required is less than twice the amount of the protein of the selected protein
- 30   or proteins that is required, then the second protein is said to specifically bind to an antibody generated to the immunogen.

It is understood that these cytokine receptor proteins are members of a family of homologous proteins

35   that comprise at least 6 so far identified genes. For a particular gene product, such as the DCRS1, the term refers not only to the amino acid sequences disclosed herein, but also to other proteins that are allelic, non-

allelic, or species variants. It is also understood that the terms include nonnatural mutations introduced by deliberate mutation using conventional recombinant technology such as single site mutation, or by excising short sections of DNA encoding the respective proteins, or by substituting new amino acids, or adding new amino acids. Such minor alterations typically will substantially maintain the immunoidentity of the original molecule and/or its biological activity. Thus, these alterations include proteins that are specifically immunoreactive with a designated naturally occurring DCRS1 protein. The biological properties of the altered proteins can be determined by expressing the protein in an appropriate cell line and measuring the appropriate effect, e.g., upon transfected lymphocytes. Particular protein modifications considered minor would include conservative substitution of amino acids with similar chemical properties, as described above for the cytokine receptor family as a whole. By aligning a protein optimally with the protein of the cytokine receptors and by using the conventional immunoassays described herein to determine immunoidentity, one can determine the protein compositions of the invention.

While many of the descriptions above (and below) are directed to individual proteins, they may be applied to complexes, e.g., natural or functional, of proteins.

#### VII. Kits and quantitation

Both naturally occurring and recombinant forms of the cytokine receptor like molecules of this invention are particularly useful in kits and assay methods. For example, these methods would also be applied to screening for binding activity, e.g., ligands for these proteins. Several methods of automating assays have been developed in recent years so as to permit screening of tens of thousands of compounds per year. See, e.g., a BIOMEK automated workstation, Beckman Instruments, Palo Alto, California, and Fodor, et al. (1991) Science 251:767-773,

which is incorporated herein by reference. The latter describes means for testing binding by a plurality of defined polymers synthesized on a solid substrate. The development of suitable assays to screen for a ligand or  
5 agonist/antagonist homologous proteins can be greatly facilitated by the availability of large amounts of purified, soluble cytokine receptors in an active state such as is provided by this invention.

Purified DCRS1 can be coated directly onto plates  
10 for use in the aforementioned ligand screening techniques. However, non-neutralizing antibodies to these proteins can be used as capture antibodies to immobilize the respective receptor on the solid phase, useful, e.g., in diagnostic uses.

This invention also contemplates use of DCRS1, fragments thereof, peptides, and their fusion products in a variety of diagnostic kits and methods for detecting the presence of the protein or its ligand.  
Alternatively, or additionally, antibodies against the  
20 molecules may be incorporated into the kits and methods. Typically the kit will have a compartment containing either a DCRS1 peptide or gene segment or a reagent which recognizes one or the other. Typically, recognition reagents, in the case of peptide, would be a receptor or  
25 antibody, or in the case of a gene segment, would usually be a hybridization probe.

A preferred kit for determining the concentration of DCRS1 in a sample would typically comprise a labeled compound, e.g., ligand or antibody, having known binding  
30 affinity for DCRS1, a source of DCRS1 (naturally occurring or recombinant) as a positive control, and a means for separating the bound from free labeled compound, for example a solid phase for immobilizing the DCRS1 in the test sample. Compartments containing  
35 reagents, and instructions, will normally be provided. Appropriate nucleic acid or protein containing kits are also provided.

Antibodies, including antigen binding fragments, specific for mammalian DCRS1 or a peptide fragment, or receptor fragments are useful in diagnostic applications to detect the presence of elevated levels of ligand and/or its fragments. Diagnostic assays may be homogeneous (without a separation step between free reagent and antibody-antigen complex) or heterogeneous (with a separation step). Various commercial assays exist, such as radioimmunoassay (RIA), enzyme-linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), enzyme-multiplied immunoassay technique (EMIT), substrate-labeled fluorescent immunoassay (SLFIA) and the like. For example, unlabeled antibodies can be employed by using a second antibody which is labeled and which recognizes the antibody to a cytokine receptor or to a particular fragment thereof. These assays have also been extensively discussed in the literature. See, e.g., Harlow and Lane (1988) Antibodies: A Laboratory Manual, CSH., and Coligan (ed. 1991 and periodic supplements). Current Protocols In Immunology Greene/Wiley, New York.

Anti-idiotypic antibodies may have similar use to serve as agonists or antagonists of cytokine receptors. These should be useful as therapeutic reagents under appropriate circumstances.

Frequently, the reagents for diagnostic assays are supplied in kits, so as to optimize the sensitivity of the assay. For the subject invention, depending upon the nature of the assay, the protocol, and the label, either labeled or unlabeled antibody, or labeled ligand is provided. This is usually in conjunction with other additives, such as buffers, stabilizers, materials necessary for signal production such as substrates for enzymes, and the like. Preferably, the kit will also contain instructions for proper use and disposal of the contents after use. Typically the kit has compartments for each useful reagent, and will contain instructions for proper use and disposal of reagents. Desirably, the reagents are provided as a dry lyophilized powder, where

the reagents may be reconstituted in an aqueous medium having appropriate concentrations for performing the assay.

The aforementioned constituents of the diagnostic assays may be used without modification or may be modified in a variety of ways. For example, labeling may be achieved by covalently or non-covalently joining a moiety which directly or indirectly provides a detectable signal. In many of these assays, a test compound, cytokine receptor, or antibodies thereto can be labeled either directly or indirectly. Possibilities for direct labeling include label groups: radiolabels such as  $^{125}\text{I}$ , enzymes (U.S. Pat. No. 3,645,090) such as peroxidase and alkaline phosphatase, and fluorescent labels (U.S. Pat. No. 3,940,475) capable of monitoring the change in fluorescence intensity, wavelength shift, or fluorescence polarization. Both of the patents are incorporated herein by reference. Possibilities for indirect labeling include biotinylation of one constituent followed by binding to avidin coupled to one of the above label groups.

There are also numerous methods of separating the bound from the free ligand, or alternatively the bound from the free test compound. The cytokine receptor can be immobilized on various matrixes followed by washing. Suitable matrices include plastic such as an ELISA plate, filters, and beads. Methods of immobilizing the receptor to a matrix include, without limitation, direct adhesion to plastic, use of a capture antibody, chemical coupling, and biotin-avidin. The last step in this approach involves the precipitation of antibody/antigen complex by any of several methods including those utilizing, e.g., an organic solvent such as polyethylene glycol or a salt such as ammonium sulfate. Other suitable separation techniques include, without limitation, the fluorescein antibody magnetizable particle method described in Rattle, et al. (1984) Clin. Chem. 30(9):1457-1461, and the double antibody magnetic particle separation as

described in U.S. Pat. No. 4,659,678, each of which is incorporated herein by reference.

The methods for linking protein or fragments to various labels have been extensively reported in the literature and do not require detailed discussion here. Many of the techniques involve the use of activated carboxyl groups either through the use of carbodiimide or active esters to form peptide bonds, the formation of thioethers by reaction of a mercapto group with an activated halogen such as chloroacetyl, or an activated olefin such as maleimide, for linkage, or the like. Fusion proteins will also find use in these applications.

Another diagnostic aspect of this invention involves use of oligonucleotide or polynucleotide sequences taken from the sequence of an cytokine receptor. These sequences can be used as probes for detecting levels of the respective cytokine receptor in patients suspected of having an immunological disorder. The preparation of both RNA and DNA nucleotide sequences, the labeling of the sequences, and the preferred size of the sequences has received ample description and discussion in the literature. Normally an oligonucleotide probe should have at least about 14 nucleotides, usually at least about 18 nucleotides, and the polynucleotide probes may be up to several kilobases. Various labels may be employed, most commonly radionuclides, particularly  $^{32}\text{P}$ . However, other techniques may also be employed, such as using biotin modified nucleotides for introduction into a polynucleotide. The biotin then serves as the site for binding to avidin or antibodies, which may be labeled with a wide variety of labels, such as radionuclides, fluorescers, enzymes, or the like. Alternatively, antibodies may be employed which can recognize specific duplexes, including DNA duplexes, RNA duplexes, DNA-RNA hybrid duplexes, or DNA-protein duplexes. The antibodies in turn may be labeled and the assay carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of



antibody bound to the duplex can be detected. The use of probes to the novel anti-sense RNA may be carried out in conventional techniques such as nucleic acid hybridization, plus and minus screening, recombinational probing, hybrid released translation (HRT), and hybrid arrested translation (HART). This also includes amplification techniques such as polymerase chain reaction (PCR).

Diagnostic kits which also test for the qualitative or quantitative presence of other markers are also contemplated. Diagnosis or prognosis may depend on the combination of multiple indications used as markers. Thus, kits may test for combinations of markers. See, e.g., Viallet, et al. (1989) Progress in Growth Factor Res. 1:89-97.

#### VIII. Therapeutic Utility

This invention provides reagents with significant therapeutic value. See, e.g., Levitzki (1996) Curr. Opin. Cell Biol. 8:239-244. The cytokine receptors (naturally occurring or recombinant), fragments thereof, mutein receptors, and antibodies, along with compounds identified as having binding affinity to the receptors or antibodies, should be useful in the treatment of conditions exhibiting abnormal expression of the receptors of their ligands. Such abnormality will typically be manifested by immunological disorders. Additionally, this invention should provide therapeutic value in various diseases or disorders associated with abnormal expression or abnormal triggering of response to the ligand. For example, the IL-1 ligands have been suggested to be involved in morphologic development, e.g., dorso-ventral polarity determination, and immune responses, particularly the primitive innate responses. See, e.g., Sun, et al. (1991) Eur. J. Biochem. 196:247-254; and Hultmark (1994) Nature 367:116-117.

Recombinant cytokine receptors, muteins, agonist or antagonist antibodies thereto, or antibodies can be

purified and then administered to a patient. These reagents can be combined for therapeutic use with additional active ingredients, e.g., in conventional pharmaceutically acceptable carriers or diluents, along  
5 with physiologically innocuous stabilizers and excipients. These combinations can be sterile, e.g., filtered, and placed into dosage forms as by lyophilization in dosage vials or storage in stabilized aqueous preparations. This invention also contemplates  
10 use of antibodies or binding fragments thereof which are not complement binding.

Ligand screening using cytokine receptor or fragments thereof can be performed to identify molecules having binding affinity to the receptors. Subsequent  
15 biological assays can then be utilized to determine if a putative ligand can provide competitive binding, which can block intrinsic stimulating activity. Receptor fragments can be used as a blocker or antagonist in that it blocks the activity of ligand. Likewise, a compound  
20 having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of ligand, e.g., inducing signaling. This invention further contemplates the therapeutic use of antibodies to cytokine receptors as antagonists.

25 The quantities of reagents necessary for effective therapy will depend upon many different factors, including means of administration, target site, reagent physiological life, pharmacological life, physiological state of the patient, and other medicants administered.  
30 Thus, treatment dosages should be titrated to optimize safety and efficacy. Typically, dosages used in vitro may provide useful guidance in the amounts useful for in situ administration of these reagents. Animal testing of effective doses for treatment of particular disorders  
35 will provide further predictive indication of human dosage. Various considerations are described, e.g., in Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon

- Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; each of which is hereby incorporated herein by reference. Methods for administration are discussed therein and below, e.g., for
- 5 oral, intravenous, intraperitoneal, or intramuscular administration, transdermal diffusion, and others. Pharmaceutically acceptable carriers will include water, saline, buffers, and other compounds described, e.g., in the Merck Index, Merck & Co., Rahway, New Jersey.
- 10 Because of the likely high affinity binding, or turnover numbers, between a putative ligand and its receptors, low dosages of these reagents would be initially expected to be effective. And the signaling pathway suggests
- 15 extremely low amounts of ligand may have effect. Thus, dosage ranges would ordinarily be expected to be in amounts lower than 1 mM concentrations, typically less than about 10  $\mu$ M concentrations, usually less than about 100 nM, preferably less than about 10 pM (picomolar), and most preferably less than about 1 fM (femtomolar), with
- 20 an appropriate carrier. Slow release formulations, or slow release apparatus will often be utilized for continuous administration.

Cytokine receptors, fragments thereof, and antibodies or its fragments, antagonists, and agonists,

25 may be administered directly to the host to be treated or, depending on the size of the compounds, it may be desirable to conjugate them to carrier proteins such as ovalbumin or serum albumin prior to their administration. Therapeutic formulations may be administered in many

30 conventional dosage formulations. While it is possible for the active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation. Formulations comprise at least one active ingredient, as defined above, together with one or more acceptable

35 carriers thereof. Each carrier must be both pharmaceutically and physiologically acceptable in the sense of being compatible with the other ingredients and not injurious to the patient. Formulations include those

suitable for oral, rectal, nasal, or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The formulations may conveniently be presented in unit dosage form and may be prepared by methods well known in the art of pharmacy. See, e.g., Gilman, et al. (eds. 1990) Goodman and Gilman's: The Pharmacological Bases of Therapeutics, 8th Ed., Pergamon Press; and Remington's Pharmaceutical Sciences, 17th ed. (1990), Mack Publishing Co., Easton, Penn.; Avis, et al. (eds. 1993) Pharmaceutical Dosage Forms: Parenteral Medications Dekker, NY; Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Tablets Dekker, NY; and Lieberman, et al. (eds. 1990) Pharmaceutical Dosage Forms: Disperse Systems Dekker, NY.

The therapy of this invention may be combined with or used in association with other therapeutic agents, particularly agonists or antagonists of other cytokine receptor family members.

#### IX. Screening

Drug screening using DCRS1 or fragments thereof can be performed to identify compounds having binding affinity to the receptor subunit, including isolation of associated components. Subsequent biological assays can then be utilized to determine if the compound has intrinsic stimulating activity and is therefore a blocker or antagonist in that it blocks the activity of the ligand. Likewise, a compound having intrinsic stimulating activity can activate the receptor and is thus an agonist in that it simulates the activity of a cytokine ligand. This invention further contemplates the therapeutic use of antibodies to the receptor as cytokine agonists or antagonists.

Similarly, complexes comprising multiple proteins may be used to screen for ligands or reagents capable of recognizing the complex. Most cytokine receptors comprise at least two subunits, which may be the same, or distinct. Alternatively, the transmembrane receptor may

bind to a complex comprising a cytokine-like ligand associated with another soluble protein serving, e.g., as a second receptor subunit. In such a case, the DCRS1 may bind to a complex of the IL-B30 with the DSRS1.

- 5        One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant DNA molecules expressing the DCRS1 in combination with the DSRS1. Cells may be isolated which express a receptor in isolation from other functional
- 10 receptors. Such cells, either in viable or fixed form, can be used for standard antibody/antigen or ligand/receptor binding assays. See also, Parce, et al. (1989) Science 246:243-247; and Owicki, et al. (1990) Proc. Nat'l Acad. Sci. USA 87:4007-4011, which describe
- 15 sensitive methods to detect cellular responses. Competitive assays are particularly useful, where the cells (source of putative ligand) are contacted and incubated with a labeled receptor or antibody having known binding affinity to the ligand, such as  $^{125}\text{I}$ -
- 20 antibody, and a test sample whose binding affinity to the binding composition is being measured. The bound and free labeled binding compositions are then separated to assess the degree of ligand binding. The amount of test compound bound is inversely proportional to the amount of
- 25 labeled receptor binding to the known source. Many techniques can be used to separate bound from free ligand to assess the degree of ligand binding. This separation step could typically involve a procedure such as adhesion to filters followed by washing, adhesion to plastic
- 30 followed by washing, or centrifugation of the cell membranes. Viable cells could also be used to screen for the effects of drugs on cytokine mediated functions, e.g., second messenger levels, i.e.,  $\text{Ca}^{++}$ ; cell proliferation; inositol phosphate pool changes; and
- 35 others. Some detection methods allow for elimination of a separation step, e.g., a proximity sensitive detection system. Calcium sensitive dyes will be useful for

detecting  $\text{Ca}^{++}$  levels, with a fluorimeter or a fluorescence cell sorting apparatus.

#### X. Ligands

5       The descriptions of the DCRS1 herein provide means to identify ligands, as described above. Such ligand should bind specifically to the respective receptor with reasonably high affinity. Various constructs are made available which allow either labeling of the receptor to  
10 detect its ligand. For example, directly labeling cytokine receptor, fusing onto it markers for secondary labeling, e.g., FLAG or other epitope tags, etc., will allow detection of receptor. This can be histological, as an affinity method for biochemical purification, or  
15 labeling or selection in an expression cloning approach. A two-hybrid selection system may also be applied making appropriate constructs with the available cytokine receptor sequences. See, e.g., Fields and Song (1989) Nature 340:245-246.

20       Generally, descriptions of cytokine receptors will be analogously applicable to individual specific embodiments directed to DCRS1 reagents and compositions. Alternatively, the DCRS1 might bind to a soluble complex of the DSRS1 with another ligand. Thus, expression  
25 cloning of a cotransfectant of a library with the DSRS1 may express combinations of the DSRS1 with cytokine-like ligand, to form the soluble complex, which binds to the DCRS1.

30       The broad scope of this invention is best understood with reference to the following examples, which are not intended to limit the inventions to the specific embodiments.

## EXAMPLES

## I. General Methods

Some of the standard methods are described or  
5 referenced, e.g., in Maniatis, et al. (1982) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor Press; Sambrook, et al. (1989) Molecular Cloning: A Laboratory Manual, (2d ed.), vols. 1-3, CSH Press, NY; Ausubel, et al., Biology,  
10 Greene Publishing Associates, Brooklyn, NY; or Ausubel, et al. (1987 and Supplements) Current Protocols in Molecular Biology, Greene/Wiley, New York. Methods for protein purification include such methods as ammonium sulfate precipitation, column chromatography,  
15 electrophoresis, centrifugation, crystallization, and others. See, e.g., Ausubel, et al. (1987 and periodic supplements); Coligan, et al. (ed. 1996) and periodic supplements, Current Protocols In Protein Science Greene/Wiley, New York; Deutscher (1990) "Guide to  
20 Protein Purification" in Methods in Enzymology, vol. 182, and other volumes in this series; and manufacturer's literature on use of protein purification products, e.g., Pharmacia, Piscataway, N.J., or Bio-Rad, Richmond, CA. Combination with recombinant techniques allow fusion to  
25 appropriate segments, e.g., to a FLAG sequence or an equivalent which can be fused via a protease-removable sequence. See, e.g., Hochuli (1989) Chemische Industrie 12:69-70; Hochuli (1990) "Purification of Recombinant Proteins with Metal Chelate Absorbent" in Setlow (ed.)  
30 Genetic Engineering, Principle and Methods 12:87-98, Plenum Press, N.Y.; and Crowe, et al. (1992) QIAexpress: The High Level Expression & Protein Purification System. QUIAGEN, Inc., Chatsworth, CA.

Computer sequence analysis is performed, e.g., using  
35 available software programs, including those from the GCG (U. Wisconsin) and GenBank sources. Public sequence databases were also used, e.g., from GenBank and others.

Many techniques applicable to IL-10 or IL-12 receptors may be applied to the DCRS1, as described, e.g., in USSN 08/110,683 (IL-10 receptor), which is incorporated herein by reference.

5

## II. Computational Analysis

Human sequences related to cytokine receptors were identified from genomic sequence database using, e.g., the BLAST server (Altschul, et al. (1994) Nature Genet. 6:119-129). Standard analysis programs may be used to evaluate structure, e.g., PHD (Rost and Sander (1994) Proteins 19:55-72) and DSC (King and Sternberg (1996) Protein Sci. 5:2298-2310). Standard comparison software includes, e.g., Altschul, et al. (1990) J. Mol. Biol. 215:403-10; Waterman (1995) Introduction to Computational Biology: Maps, Sequences, and Genomes Chapman & Hall; Lander and Waterman (eds. 1995) Calculating the Secrets of Life: Applications of the Mathematical Sciences in Molecular Biology National Academy Press; and Speed and Waterman (eds. 1996) Genetic Mapping and DNA Sequencing (Ima Volumes in Mathematics and Its Applications, Vol 81) Springer Verlag.

## III. Cloning of full-length DCRS1 cDNAs; Chromosomal localization

PCR primers derived from the DCRS1 sequence are used to probe a human cDNA library. Sequences may be derived, e.g., from Table 1, preferably those adjacent the ends of incomplete sequences. Full length cDNAs for primate, rodent, or other species DCRS1 are cloned, e.g., by DNA hybridization screening of  $\lambda$ gt10 phage. PCR reactions are conducted using T. aquaticus Taqplus DNA polymerase (Stratagene) under appropriate conditions.

Chromosome spreads are prepared. In situ hybridization is performed on chromosome preparations obtained from phytohemagglutinin-stimulated human lymphocytes cultured for 72 h. 5-bromodeoxyuridine was added for the final seven hours of culture (60  $\mu$ g/ml of



medium), to ensure a posthybridization chromosomal banding of good quality.

A PCR fragment, amplified with the help of primers, is cloned into an appropriate vector. The vector is  
5 labeled by nick-translation with  $^3\text{H}$ . The radiolabeled probe is hybridized to metaphase spreads at final concentration of 200 ng/ml of hybridization solution as described in Mattei, et al. (1985) Hum. Genet. 69:327-331.

10 After coating with nuclear track emulsion (KODAK NTB2), slides are exposed. To avoid any slipping of silver grains during the banding procedure, chromosome spreads are first stained with buffered Giemsa solution and metaphase photographed. R-banding is then performed  
15 by the fluorochrome-photolysis-Giemsa (FPG) method and metaphases rephotographed before analysis.

Similar appropriate methods are used for other species.

#### 20 IV. Localization of DCRS1 mRNA

Human multiple tissue (Cat# 1, 2) and cancer cell line blots (Cat# 7757-1), containing approximately 2  $\mu\text{g}$  of poly(A)<sup>+</sup> RNA per lane, are purchased from Clontech (Palo Alto, CA). Probes are radiolabeled with [ $\alpha$ - $^{32}\text{P}$ ]  
25 dATP, e.g., using the Amersham Rediprime random primer labeling kit (RPN1633). Prehybridization and hybridizations are performed at 65° C in 0.5 M Na<sub>2</sub>HPO<sub>4</sub>, 7% SDS, 0.5 M EDTA (pH 8.0). High stringency washes are conducted, e.g., at 65° C with two initial washes in 2 x  
30 SSC, 0.1% SDS for 40 min followed by a subsequent wash in 0.1 x SSC, 0.1% SDS for 20 min. Membranes are then exposed at -70° C to X-Ray film (Kodak) in the presence of intensifying screens. More detailed studies by cDNA library Southern are performed with selected human DCRS1  
35 clones to examine their expression in hemopoietic or other cell subsets.

Alternatively, two appropriate primers are selected from Table 1. RT-PCR is used on an appropriate mRNA

sample selected for the presence of message to produce a cDNA, e.g., a sample which expresses the gene.

Full length clones may be isolated by hybridization of cDNA libraries from appropriate tissues pre-selected  
5 by PCR signal. Northern blots can be performed.

Message for genes encoding DCRS1 will be assayed by appropriate technology, e.g., PCR, immunoassay, hybridization, or otherwise. Tissue and organ cDNA preparations are available, e.g., from Clontech, Mountain  
10 View, CA. Identification of sources of natural expression are useful, as described. And the identification of functional receptor subunit pairings will allow for prediction of what cells express the combination of receptor subunits which will result in a  
15 physiological responsiveness to each of the cytokine ligands.

For mouse distribution, e.g., Southern Analysis can be performed: DNA (5 µg) from a primary amplified cDNA library was digested with appropriate restriction enzymes to release  
20 the inserts, run on a 1% agarose gel and transferred to a nylon membrane (Schleicher and Schuell, Keene, NH).

Samples for mouse mRNA isolation may include:  
resting mouse fibroblastic L cell line (C200); Braf:ER (Braf fusion to estrogen receptor) transfected cells,  
25 control (C201); T cells, TH1 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IFN-γ and anti IL-4; T200); T cells, TH2 polarized (Mel14 bright, CD4+ cells from spleen, polarized for 7 days with IL-4 and anti-IFN-γ; T201); T cells, highly TH1 polarized  
30 (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T202); T cells, highly TH2 polarized (see Openshaw, et al. (1995) J. Exp. Med. 182:1357-1367; activated with anti-CD3 for 2, 6, 16 h pooled; T203); CD44- CD25+ pre T cells, sorted  
35 from thymus (T204); TH1 T cell clone D1.1, resting for 3 weeks after last stimulation with antigen (T205); TH1 T cell clone D1.1, 10 µg/ml ConA stimulated 15 h (T206); TH2 T cell clone CDC35, resting for 3 weeks after last

stimulation with antigen (T207); TH2 T cell clone CDC35, 10 µg/ml ConA stimulated 15 h (T208); Mel14+ naive T cells from spleen, resting (T209); Mel14+ T cells, polarized to Th1 with IFN-γ/IL-12/anti-IL-4 for 6, 12, 24 h pooled (T210); Mel14+ T cells, polarized to Th2 with IL-4/anti-IFN-γ for 6, 13, 24 h pooled (T211); unstimulated mature B cell leukemia cell line A20 (B200); unstimulated B cell line CH12 (B201); unstimulated large B cells from spleen (B202); B cells from total spleen, LPS activated (B203); metrizamide enriched dendritic cells from spleen, resting (D200); dendritic cells from bone marrow, resting (D201); monocyte cell line RAW 264.7 activated with LPS 4 h (M200); bone-marrow macrophages derived with GM and M-CSF (M201); macrophage cell line J774, resting (M202); macrophage cell line J774 + LPS + anti-IL-10 at 0.5, 1, 3, 6, 12 h pooled (M203); macrophage cell line J774 + LPS + IL-10 at 0.5, 1, 3, 5, 12 h pooled (M204); aerosol challenged mouse lung tissue, Th2 primers, aerosol OVA challenge 7, 14, 23 h pooled (see Garlisi, et al. (1995) Clinical Immunology and Immunopathology 75:75-83; X206); Nippostrongylus-infected lung tissue (see Coffman, et al. (1989) Science 245:308-310; X200); total adult lung, normal (O200); total lung, rag-1 (see Schwarz, et al. (1993) Immunodeficiency 4:249-252; O205); IL-10 K.O. spleen (see Kuhn, et al. (1991) Cell 75:263-274; X201); total adult spleen, normal (O201); total spleen, rag-1 (O207); IL-10 K.O. Peyer's patches (O202); total Peyer's patches, normal (O210); IL-10 K.O. mesenteric lymph nodes (X203); total mesenteric lymph nodes, normal (O211); IL-10 K.O. colon (X203); total colon, normal (O212); NOD mouse pancreas (see Makino, et al. (1980) Jikken Dobutsu 29:1-13; X205); total thymus, rag-1 (O208); total kidney, rag-1 (O209); total heart, rag-1 (O202); total brain, rag-1 (O203); total testes, rag-1 (O204); total liver, rag-1 (O206); rat normal joint tissue (O300); and rat arthritic joint tissue (X300).

Samples for human mRNA isolation may include:

peripheral blood mononuclear cells (monocytes, T cells, NK cells, granulocytes, B cells), resting (T100);

peripheral blood mononuclear cells, activated with anti-CD3 for 2, 6, 12 h pooled (T101); T cell, TH0 clone Mot 72, resting (T102); T cell, TH0 clone Mot 72, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T103); T cell, TH0 clone Mot 72, anergic treated with specific peptide for 2, 7, 12 h pooled (T104); T cell, TH1 clone HY06, resting (T107); T cell, TH1 clone HY06, activated with anti-CD28 and anti-CD3 for 3, 6, 12 h pooled (T108); T cell, TH1 clone HY06, anergic treated with specific peptide for 2, 6, 12 h pooled (T109); T cell, TH2 clone HY935, resting (T110); T cell, TH2 clone HY935, activated with anti-CD28 and anti-CD3 for 2, 7, 12 h pooled (T111); T cells CD4+CD45RO- T cells polarized 27 days in anti-CD28, IL-4, and anti IFN- $\gamma$ , TH2 polarized, activated with anti-CD3 and anti-CD28 4 h (T116); T cell tumor lines Jurkat and Hut78, resting (T117); T cell clones, pooled AD130.2, Tc783.12, Tc783.13, Tc783.58, Tc782.69, resting (T118); T cell random  $\gamma\delta$  T cell clones, resting (T119); Splenocytes, resting (B100); Splenocytes, activated with anti-CD40 and IL-4 (B101); B cell EBV lines pooled WT49, RSB, JY, CVIR, 721.221, RM3, HSY, resting (B102); B cell line JY, activated with PMA and ionomycin for 1, 6 h pooled (B103); NK 20 clones pooled, resting (K100); NK 20 clones pooled, activated with PMA and ionomycin for 6 h (K101); NKL clone, derived from peripheral blood of LGL leukemia patient, IL-2 treated (K106); NK cytotoxic clone 640-A30-1, resting (K107); hematopoietic precursor line TF1, activated with PMA and ionomycin for 1, 6 h pooled (C100); U937 premonocytic line, resting (M100); U937 premonocytic line, activated with PMA and ionomycin for 1, 6 h pooled (M101); elutriated monocytes, activated with LPS, IFN $\gamma$ , anti-IL-10 for 1, 2, 6, 12, 24 h pooled (M102); elutriated monocytes, activated with LPS, IFN $\gamma$ , IL-10 for 1, 2, 6, 12, 24 h pooled (M103); elutriated monocytes, activated with LPS, IFN $\gamma$ , anti-IL-10 for 4, 16

- h pooled (M106); elutriated monocytes, activated with LPS, IFN $\gamma$ , IL-10 for 4, 16 h pooled (M107); elutriated monocytes, activated LPS for 1 h (M108); elutriated monocytes, activated LPS for 6 h (M109); DC 70% CD1a+, from CD34+ GM-CSF, TNF $\alpha$  12 days, resting (D101); DC 70% CD1a+, from CD34+ GM-CSF, TNF $\alpha$  12 days, activated with PMA and ionomycin for 1 hr (D102); DC 70% CD1a+, from CD34+ GM-CSF, TNF $\alpha$  12 days, activated with PMA and ionomycin for 6 hr (D103); DC 95% CD1a+, from CD34+ GM-CSF, TNF $\alpha$  12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D104); DC 95% CD14+, ex CD34+ GM-CSF, TNF $\alpha$  12 days FACS sorted, activated with PMA and ionomycin 1, 6 hr pooled (D105); DC CD1a+ CD86+, from CD34+ GM-CSF, TNF $\alpha$  12 days FACS sorted, activated with PMA and ionomycin for 1, 6 h pooled (D106); DC from monocytes GM-CSF, IL-4 5 days, resting (D107); DC from monocytes GM-CSF, IL-4 5 days, resting (D108); DC from monocytes GM-CSF, IL-4 5 days, activated LPS 4, 16 h pooled (D109); DC from monocytes GM-CSF, IL-4 5 days, activated TNF $\alpha$ , monocyte supe for 4, 16 h pooled (D110); leiomyoma L11 benign tumor (X101); normal myometrium M5 (O115); malignant leiomyosarcoma GS1 (X103); lung fibroblast sarcoma line MRC5, activated with PMA and ionomycin for 1, 6 h pooled (C101); kidney epithelial carcinoma cell line CHA, activated with PMA and ionomycin for 1, 6 h pooled (C102); kidney fetal 28 wk male (O100); lung fetal 28 wk male (O101); liver fetal 28 wk male (O102); heart fetal 28 wk male (O103); brain fetal 28 wk male (O104); gallbladder fetal 28 wk male (O106); small intestine fetal 28 wk male (O107); adipose tissue fetal 28 wk male (O108); ovary fetal 25 wk female (O109); uterus fetal 25 wk female (O110); testes fetal 28 wk male (O111); spleen fetal 28 wk male (O112); adult placenta 28 wk (O113); and tonsil inflamed, from 12 year old (X100).
- Similar samples may isolated in other species for evaluation.

#### V. Cloning of species counterparts of DCRS1

Various strategies are used to obtain species counterparts of the DCRS1, preferably from other primates or rodents. One method is by cross hybridization using  
5 closely related species DNA probes. It may be useful to go into evolutionarily similar species as intermediate steps. Another method is by using specific PCR primers based on the identification of blocks of similarity or difference between genes, e.g., areas of highly conserved  
10 or nonconserved polypeptide or nucleotide sequence.

#### VI. Production of mammalian DCRS1 protein

An appropriate, e.g., GST, fusion construct is engineered for expression, e.g., in *E. coli*. For  
15 example, a mouse IGIF pGex plasmid is constructed and transformed into *E. coli*. Freshly transformed cells are grown, e.g., in LB medium containing 50 µg/ml ampicillin and induced with IPTG (Sigma, St. Louis, MO). After overnight induction, the bacteria are harvested and the  
20 pellets containing the DCRS1 protein are isolated. The pellets are homogenized, e.g., in TE buffer (50 mM Tris-base pH 8.0, 10 mM EDTA and 2 mM pefabloc) in 2 liters. This material is passed through a microfluidizer (Microfluidics, Newton, MA) three times. The fluidized  
25 supernatant is spun down on a Sorvall GS-3 rotor for 1 h at 13,000 rpm. The resulting supernatant containing the cytokine receptor protein is filtered and passed over a glutathione-SEPHAROSE column equilibrated in 50 mM Tris-base pH 8.0. The fractions containing the DCRS1-GST  
30 fusion protein are pooled and cleaved, e.g., with thrombin (Enzyme Research Laboratories, Inc., South Bend, IN). The cleaved pool is then passed over a Q-SEPHAROSE column equilibrated in 50 mM Tris-base. Fractions containing DCRS1 are pooled and diluted in cold distilled  
35 H<sub>2</sub>O, to lower the conductivity, and passed back over a fresh Q-Sepharose column, alone or in succession with an immunoaffinity antibody column. Fractions containing the

DCRS1 protein are pooled, aliquoted, and stored in the -70° C freezer.

Comparison of the CD spectrum with cytokine receptor protein may suggest that the protein is correctly folded.

5 See Hazuda, et al. (1969) J. Biol. Chem. 264:1689-1693.

#### VII. Determining physiological forms of receptors

The cellular forms of receptors for ligands can be tested with the various ligands and receptor subunits  
10 provided. In particular, multiple cytokine receptor like ligands have been identified. The IL-B30 cytokine has been described. See above.

Cotransformation of the DCRS1 with putative other receptor subunits may be performed. In particular, the  
15 DSRS1 is suggested to be a second receptor subunit needed for functional receptor signaling. Such cells may be used to screen putative cytokine ligands, such as the IL-B30, for signaling. A cell proliferation assay may be used. In fact, the DSRS1 may combine with the IL-B30 to  
20 form a soluble cytokine-receptor subunit complex, which then binds to the DCRS1.

In addition, it has been known that many cytokine receptors function as heterodimers. The IL-1 $\alpha$  and IL-1 $\beta$  ligands bind an IL-1R1 as the primary receptor and this  
25 complex then forms a high affinity receptor complex with the IL-1R3. As indicated above, the sequence similarity to IL-12 receptor subunits suggests functional similarity of the functional receptor, e.g., a soluble alpha subunit, and transmembrane beta subunit.

30 These subunit combinations can be tested now with the provided reagents. In particular, appropriate constructs can be made for transformation or transfection of subunits into cells. Constructs for the alpha chains, e.g., DSRS1 forms, can be made. Likewise for the beta  
35 subunit DCRS1. Combinatorial transfections of transformations can make cells expressing defined subunits, which can be tested for response to the predicted ligands. Appropriate cell types can be used,

e.g., 293 T cells, with, e.g., an NF $\kappa$ B reporter construct.

Biological assays will generally be directed to the ligand binding feature of the protein or to the kinase/phosphatase activity of the receptor. The activity will typically be reversible, as are many other enzyme reactions, and may mediate phosphatase or phosphorylase activities, which activities are easily measured by standard procedures. See, e.g., Hardie, et al. (eds. 1995) The Protein Kinase FactBook vols. I and II, Academic Press, San Diego, CA; Hanks, et al. (1991) Meth. Enzymol. 200:38-62; Hunter, et al. (1992) Cell 70:375-388; Lewin (1990) Cell 61:743-752; Pines, et al. (1991) Cold Spring Harbor Symp. Quant. Biol. 56:449-463; and Parker, et al. (1993) Nature 363:736-738.

The family of cytokines contains molecules which are important mediators of hematopoiesis or inflammatory disease. See, e.g., Thomson (ed. 1994) The Cytokine Handbook Academic Press, San Diego; and Dinarello (1996) Blood 87:2095-2147.

#### VIII. Preparation of antibodies specific for DCRS1

Inbred Balb/c mice are immunized intraperitoneally with recombinant forms of the protein, e.g., purified DCRS1 or stable transfected NIH-3T3 cells. Animals are boosted at appropriate time points with protein, with or without additional adjuvant, to further stimulate antibody production. Serum is collected, or hybridomas produced with harvested spleens.

Alternatively, Balb/c mice are immunized with cells transformed with the gene or fragments thereof, either endogenous or exogenous cells, or with isolated membranes enriched for expression of the antigen. Serum is collected at the appropriate time, typically after numerous further administrations. Various gene therapy techniques may be useful, e.g., in producing protein in situ, for generating an immune response. Serum or antibody preparations may be cross-absorbed or



immunoselected to prepare substantially purified antibodies of defined specificity and high affinity.

Monoclonal antibodies may be made. For example, splenocytes are fused with an appropriate fusion partner and hybridomas are selected in growth medium by standard procedures. Hybridoma supernatants are screened for the presence of antibodies which bind to the DCRS1, e.g., by ELISA or other assay. Antibodies which specifically recognize specific DCRS1 embodiments may also be selected or prepared.

In another method, synthetic peptides or purified protein are presented to an immune system to generate monoclonal or polyclonal antibodies. See, e.g., Coligan (ed. 1991) Current Protocols in Immunology Wiley/Greene; and Harlow and Lane (1989) Antibodies: A Laboratory Manual Cold Spring Harbor Press. In appropriate situations, the binding reagent is either labeled as described above, e.g., fluorescence or otherwise, or immobilized to a substrate for panning methods. Nucleic acids may also be introduced into cells in an animal to produce the antigen, which serves to elicit an immune response. See, e.g., Wang, et al. (1993) Proc. Nat'l. Acad. Sci. 90:4156-4160; Barry, et al. (1994) BioTechniques 16:616-619; and Xiang, et al. (1995) Immunity 2: 129-135.

Moreover, antibodies which may be useful to determine the combination of the DCRS1 with a functional alpha subunit may be generated. Thus, e.g., epitopes characteristic of a particular functional alpha/beta combination may be identified with appropriate antibodies.

#### IX. Production of fusion proteins with DCRS1

Various fusion constructs are made with DCRS1. A portion of the appropriate gene is fused to an epitope tag, e.g., a FLAG tag, or to a two hybrid system construct. See, e.g., Fields and Song (1989) Nature 340:245-246.

The epitope tag may be used in an expression cloning procedure with detection with anti-FLAG antibodies to detect a binding partner, e.g., ligand for the respective cytokine receptor. The two hybrid system may also be  
5 used to isolate proteins which specifically bind to DCRS1.

#### X. Structure activity relationship

Information on the criticality of particular  
10 residues is determined using standard procedures and analysis. Standard mutagenesis analysis is performed, e.g., by generating many different variants at determined positions, e.g., at the positions identified above, and evaluating biological activities of the variants. This  
15 may be performed to the extent of determining positions which modify activity, or to focus on specific positions to determine the residues which can be substituted to either retain, block, or modulate biological activity.

Alternatively, analysis of natural variants can  
20 indicate what positions tolerate natural mutations. This may result from populational analysis of variation among individuals, or across strains or species. Samples from selected individuals are analyzed, e.g., by PCR analysis and sequencing. This allows evaluation of population  
25 polymorphisms.

#### XI. Isolation of a ligand for DCRS1

A cytokine receptor can be used as a specific binding reagent to identify its binding partner, by  
30 taking advantage of its specificity of binding, much like an antibody would be used. The binding receptor may be a heterodimer of receptor subunits; or may involve, e.g., a complex of the DCRS1 with DSRS1. A binding reagent is either labeled as described above, e.g., fluorescence or  
35 otherwise, or immobilized to a substrate for panning methods.

- The binding composition is used to screen an expression library made from a cell line which expresses a binding partner, i.e., ligand, preferably membrane associated. Standard staining techniques are used to
- 5 detect or sort surface expressed ligand, or surface expressing transformed cells are screened by panning. Screening of intracellular expression is performed by various staining or immunofluorescence procedures. See also McMahan, et al. (1991) EMBO J. 10:2821-2832.
- 10 For example, on day 0, precoat 2-chamber permanox slides with 1 ml per chamber of fibronectin, 10 ng/ml in PBS, for 30 min at room temperature. Rinse once with PBS. Then plate COS cells at  $2-3 \times 10^5$  cells per chamber in 1.5 ml of growth media. Incubate overnight at 37° C.
- 15 On day 1 for each sample, prepare 0.5 ml of a solution of 66 µg/ml DEAE-dextran, 66 µM chloroquine, and 4 µg DNA in serum free DME. For each set, a positive control is prepared, e.g., of DCRS1-FLAG cDNA at 1 and 1/200 dilution, and a negative mock. Rinse cells with
- 20 serum free DME. Add the DNA solution and incubate 5 hr at 37° C. Remove the medium and add 0.5 ml 10% DMSO in DME for 2.5 min. Remove and wash once with DME. Add 1.5 ml growth medium and incubate overnight.
- On day 2, change the medium. On days 3 or 4, the
- 25 cells are fixed and stained. Rinse the cells twice with Hank's Buffered Saline Solution (HBSS) and fix in 4% paraformaldehyde (PFA)/glucose for 5 min. Wash 3X with HBSS. The slides may be stored at -80° C after all liquid is removed. For each chamber, 0.5 ml incubations
- 30 are performed as follows. Add HBSS/saponin (0.1%) with 32 µl/ml of 1 M  $\text{NaN}_3$  for 20 min. Cells are then washed with HBSS/saponin 1X. Add appropriate DCRS1 or DCRS1/antibody complex to cells and incubate for 30 min. Wash cells twice with HBSS/saponin. If appropriate, add
- 35 first antibody for 30 min. Add second antibody, e.g., Vector anti-mouse antibody, at 1/200 dilution, and incubate for 30 min. Prepare ELISA solution, e.g., Vector Elite ABC horseradish peroxidase solution, and

preincubate for 30 min. Use, e.g., 1 drop of solution A (avidin) and 1 drop solution B (biotin) per 2.5 ml HBSS/saponin. Wash cells twice with HBSS/saponin. Add ABC HRP solution and incubate for 30 min. Wash cells  
5 twice with HBSS, second wash for 2 min, which closes cells. Then add Vector diaminobenzoic acid (DAB) for 5 to 10 min. Use 2 drops of buffer plus 4 drops DAB plus 2 drops of H<sub>2</sub>O<sub>2</sub> per 5 ml of glass distilled water.  
Carefully remove chamber and rinse slide in water. Air  
10 dry for a few minutes, then add 1 drop of Crystal Mount and a cover slip. Bake for 5 min at 85-90° C.

Evaluate positive staining of pools and progressively subclone to isolation of single genes responsible for the binding.

15 Alternatively, receptor reagents are used to affinity purify or sort out cells expressing a putative ligand. See, e.g., Sambrook, et al. or Ausubel, et al.

Another strategy is to screen for a membrane bound receptor by panning. The receptor cDNA is constructed as  
20 described above. The ligand, e.g., either IL-B30 alone or a complex of IL-B30 with DCRS1, can be immobilized and used to immobilize expressing cells. Immobilization may be achieved by use of appropriate antibodies which recognize, e.g., a FLAG sequence of a DCRS1 fusion  
25 construct, or by use of antibodies raised against the first antibodies. Recursive cycles of selection and amplification lead to enrichment of appropriate clones and eventual isolation of receptor expressing clones.

Phage expression libraries can be screened by  
30 mammalian DCRS1. Appropriate label techniques, e.g., anti-FLAG antibodies, will allow specific labeling of appropriate clones.

All citations herein are incorporated herein by reference to the same extent as if each individual publication or patent application was specifically and  
5 individually indicated to be incorporated by reference.

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way  
10 of example only, and the invention is to be limited by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled; and the invention is not to be limited by the specific  
15 embodiments that have been presented herein by way of example.

## WHAT IS CLAIMED IS:

1. A composition comprising:
  - a) both:
    - 5 i) a DSRS1 protein; and
    - ii) an isolated or recombinant DCRS1 protein;
  - b) both:
    - i) an isolated or recombinant DSRS1 protein; and
    - 10 ii) a DCRS1 protein; or
  - c) both:
    - i) a substantially pure or recombinant IL-B30 protein; and
    - 15 ii) a DCRS1 protein.
2. The composition of Claim 1, wherein:
  - a) said DSRS1 protein has sequence of mature SEQ ID NO: 9 or 11;
  - b) said DCRS1 protein has sequence of mature SEQ ID NO: 13 or 15; or
  - 20 c) said IL-B30 has sequence of mature SEQ ID NO: 17 or 19; or
  - d) at least one of said proteins:
    - i) is unglycosylated;
    - 25 ii) is made with synthetic methods;
    - iii) has a detectable label;
    - iv) is attached to a solid substrate; or
    - v) is conjugated to another chemical moiety.
- 30 3. A composition comprising:
  - a) a substantially pure DCRS1 protein and:
    - i) a DSRS1 protein; or
    - ii) an IL-B30 cytokine protein; or
  - b) a DCRS1 protein and a substantially pure:
    - 35 i) DSRS1 protein; or
    - ii) IL-B30 cytokine protein.

4. The composition of Claim 3 comprising said DCRS1 and said DSRS1 proteins, wherein said proteins combine to bind IL-B30 with high affinity.
- 5 5. A sterile composition of Claim 3.
6. A kit comprising said proteins of Claim 3, and:
- a) a compartment comprising two or more of said proteins;
- 10 b) a compartment comprising a soluble receptor alpha subunit;
- c) a compartment comprising an IL-B30 cytokine protein; or
- d) instructions for use or disposal of reagents in
- 15 said kit.
7. A binding composition comprising the antigen binding sites from antibodies, which antibodies bind to an epitope found on a composition of Claim 1, but not on
- 20 separate proteins thereof.
8. The binding composition of Claim 7, wherein:
- a) said DCRS1 is:
- i) a primate protein;
- 25 ii) a purified human or mouse DCRS1; or
- iii) a mature polypeptide of Table 1;
- b) said DSRS1 is:
- i) a primate protein;
- ii) a purified human or mouse DSRS1; or
- 30 iii) a mature polypeptide of Table 4; or
- c) said IL-B30 is:
- i) a primate protein;
- ii) a purified human or mouse IL-B30; or
- iii) a mature polypeptide of Table 6.

9. The binding composition of Claim 7, wherein said binding composition:

- a) is in a container;
- 5 b) is an Fv, Fab, or Fab2 fragment;
- c) is conjugated to another chemical moiety;
- d) is immunoselected;
- e) is a polyclonal antibody;
- f) exhibits a Kd to antigen of at least 30  $\mu$ M;
- 10 g) is attached to a solid substrate, including a bead or plastic membrane;
- h) is in a sterile composition; or
- i) is detectably labeled, including a radioactive or fluorescent label.

15 10. A kit comprising said binding composition of Claim 7, and:

- a) a compartment comprising said binding composition;
- 20 b) a compartment comprising said DCRS1, DSRS1, or IL-B30 protein; or
- c) instructions for use or disposal of reagents in said kit.

25 11. An isolated or recombinant nucleic acid encoding:

- a) both:
  - i) a DSRS1 protein; and
  - ii) a DCRS1 protein;
- 30 b) both:
  - i) a DSRS1 protein; and
  - ii) an IL-B30 protein; or
- c) both:
  - i) a DCRS1 protein; and
  - 35 ii) an IL-B30 protein.



12. The nucleic acid of Claim 11, which encodes both a DCRS1 protein and a DSRS1 protein.
- 5 13. The nucleic acid of Claim 11, which encodes both a DSRS1 protein and an IL-B30.
14. The nucleic acid of Claim 11, which is an expression vector.
- 10 15. The nucleic acid of Claim 11, wherein:
- a) said DSRS1 protein has sequence of mature SEQ ID NO: 9 or 11;
  - b) said DCRS1 protein has sequence of mature SEQ ID NO: 13 or 15; or
  - 15 c) said IL-B30 has sequence of mature SEQ ID NO: 17 or 19.
16. The nucleic acid of Claim 11, comprising the coding portion of:
- 20
- a) SEQ ID NO: 8 or 10;
  - b) SEQ ID NO: 12 or 14; or
  - c) SEQ ID NO: 16 or 18.
- 25 17. A cell comprising said recombinant nucleic acid of Claim 11.
18. The cell of Claim 17, wherein said cell is:
- a) a prokaryotic cell;
  - 30 b) a eukaryotic cell;
  - c) a bacterial cell;
  - d) a yeast cell;
  - e) an insect cell;
  - f) a mammalian cell;
  - 35 g) a mouse cell;
  - h) a primate cell; or
  - i) a human cell.

19. A method of producing a receptor complex, comprising culturing a cell of Claim 17 in an environment resulting in expression of said DCRS1 and said DSRS1 proteins, thereby forming said receptor complex.

5

20. A method of screening for ligands for a receptor complex comprising said DCRS1 and said DSRS1 proteins, comprising screening a library of compounds for binding to said cell of Claim 17.

10

## SEQUENCE SUBMISSION

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# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/02600

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/715 C07K14/54 C07K16/24 C07K16/28  
G01N33/566

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 44455 A (ZYMOGENETICS INC) 27 November 1997 (1997-11-27) compare SEQ ID NO:5 with SEQ ID NO:13 in the present application page 3, line 12 - line 17 ---	1-6, 11-20
A	FISCHER M ET AL: "A BIOACTIVE DESIGNER CYTOKINE FOR HUMAN HEMATOPOIETIC PROGENITOR CELL EXPANSION" NATURE BIOTECHNOLOGY, vol. 15, no. 2, 1 February 1997 (1997-02-01), pages 142-145, XP002047603 ISSN: 1087-0156 page 144, last paragraph; figure 1 --- -/--	1-6, 11-20

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

13 July 1999

Date of mailing of the international search report

20/07/1999

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Cupido, M

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/02600

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 05280 A (SCHERING CORPORATION; BAZAN JF) 4 February 1999 (1999-02-04) compare SEQ ID NO:2 with SEQ ID NO:17 in this application ----	1-6, 11-20
P,A	WO 98 31811 A (DONALDSON DEBRA D ;GENETICS INST (US); COLLINS MARY (US); NEBEN TA) 23 July 1998 (1998-07-23) compare amino acid residues 18-425 in SEQ ID NO:5 with residues 9-416 in SEQ ID NO:11 of the present application ----	1-6, 11-20
P,A	WO 98 49307 A (ZYMOGENETICS INC) 5 November 1998 (1998-11-05) compare SEQ ID NO:2 with SEQ ID NO:9 of the present application ----	1-6, 11-20
P,A	WO 98 11225 A (NICOLA NICOS ANTONY ;FABRI LOUIS (AU); FARLEY ALISON (AU); NASH AN) 19 March 1998 (1998-03-19) compare SEQ ID NO:13 with SEQ ID NO:9 in the present application -----	1-6, 11-20

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/ 02600

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 7-11  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 7-11

The claimed epitope is disclosed in a manner that does not allow a meaningful search

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/02600

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9744455 A	27-11-1997	US 5792850 A AU 3009397 A EP 0910635 A	11-08-1998 09-12-1997 28-04-1999
WO 9905280 A	04-02-1999	AU 8589498 A	16-02-1999
WO 9831811 A	23-07-1998	AU 5733898 A	07-08-1998
WO 9849307 A	05-11-1998	AU 7276098 A	24-11-1998
WO 9811225 A	19-03-1998	AU 4308097 A	02-04-1998